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Remarks:

A request for correction of the claims (typographical errors claim 15) has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 3.).

(54) **ExPEC-specific proteins, genes encoding them and uses thereof**

(57) The invention relates to isolated antigenic polypeptides obtainable by a process comprising the steps of:

- 1- selecting on the basis of sequence analysis those of the polypeptides which are either located in the outer membrane or secreted by the bacteria,
- 2- identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates,
- 3- purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in B2/D

isolates,  
4- testing the polypeptides for immunogenicity using animals models.

Application for making vaccines compositions.

**EP 1 342 784 A1**

## Description

[0001] The invention relates to new products specific to pathogenic strains, particularly to extra-intestinal *E. coli* strains.

It more particularly relates as products to antigenic polypeptides and antibodies directed against said polypeptides and to their use as vaccines and in immunotherapy, respectively.

[0002] Although *Escherichia coli* is probably the best known bacterial species and is one of the most common isolates in clinical microbiology laboratories, misconceptions abound regarding the various types of *E. coli* and the infections they cause.

[0003] *E. coli* strains of biological significance to humans can be broadly considered as constituting 3 major groups:

1. Commensal strains, which are part of the normal flora.
2. Intestinal pathogenic strains, which are not part of the normal flora. This group contains various pathotypes (EPEC, EHEC, ETEC, EIEC) not including *Shigella*.
3. Extra-intestinal strains (ExPEC) which are responsible for infections outside the gastro-intestinal (GI) tract, but can also be part of the normal flora. All hosts are susceptible to these infections, immunocompromised and normal.

[0004] ExPEC strains are responsible for the majority of the urinary tract infections (UTI) particularly cystitis, pyelonephritis, and catheter associated infections.

[0005] They are also responsible for abdominal infections, nosocomial pneumoniae, neonatal meningitis, soft tissue infections, and bone infections. Each one of these localizations can lead to bacteremia with a risk of sepsis in case of organ failure. ExPEC strains are indeed the most common Gram negative bacilli isolated from blood cultures. 750 000 cases of bacterial sepsis occur each year in the US, and are responsible for 225 000 deaths. In a recent study on 1690 cases of sepsis, it was shown that the main bacteria species identified is ExPEC (16% of the cases) and then *S. aureus* (14% of the cases).

[0006] These numbers demonstrate the importance of ExPEC strains in both hospital and community acquired infections.

[0007] ExPEC strains correspond to a homogenous subset of *E. coli* strains. Analysis of phylogenetic relationships among *E. coli* strains by MLEE has revealed that *E. coli* belong to 4 main phylogenetic groups designated A, B1, B2 and D.

The pathogenesis of ExPEC strains is that of extra-cellular microorganisms, i.e., they are well adapted to growth in the extra-cellular fluids and efficiently resist phagocytosis by polymorphonuclear. Initial studies have shown that virulence factors known to be important for the extra-cellular growth are mainly found in B2/D *E. coli*, thus suggesting that B2/D subgroups contain most of the ExPEC strains. This was reinforced by experiments performed on animals showing that B2/D strains are more virulent than A and B1 strains. Subsequent epidemiological studies have indeed confirmed these hypotheses. B2/D isolates are those predominantly responsible for neonatal meningitis (87%) and community or nosocomial acquired urosepsis, (93 % and 85%, respectively). Surprisingly, similar results have been reported for cystitis (70% are due to the sole B2 *E. coli*), thus demonstrating that the pathogenesis of ExPEC strains is that of extra-cellular organisms.

These recent findings demonstrate that the B2/D subgroup of strains is the *E. coli* core genome the best adapted to growth in extra-cellular fluids.

[0008] In addition to this core genome, ExPEC strains have various pathogenicity islands which encode virulence factors associated with the different pathogenesis of extra-intestinal *E. coli* infections (UTI, urosepsis, neonatal meningitis...). Among the main virulence factors are the capsule, which is well-known to be important for extra-cellular growth, and the iron chelation systems (aerobactin and enterochelin, for example). In addition, depending on the pathogenesis, these strains can produce toxins (CNF, hemolysin...), adhesins (pap, sfa...) and other iron chelation system.

[0009] The notion that B2/D *E. coli* correspond to a distinct subset of pathogenic *E. coli* strains is reinforced by the fact that B2/D *E. coli* are not broadly isolated from the stools of humans. They were recovered from only 11% of individuals, whereas A and B1 subgroups are present in the stools of 74% of the individuals of a human population.

[0010] As mentioned above the pathogenesis of ExPEC strains relies on their ability to multiply in the extra-cellular fluids and to resist bactericidal activity of the complement and phagocytosis by polymorphonuclear. Therefore, as for other extra-cellular pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae* and *meningitidis*) a protective antigen against ExPEC has to induce antibodies that promote opsonisation and/or the bactericidal activity of serum.

[0011] Considering the above statements, an efficient antigen has to be largely represented among the population of B2/D *E. coli*. Similarly to other extra-cellular pathogens, the capsular polysaccharide would be an ideal antigen, however most pathogenic B2 strains express the K1 polysaccharide. The latter has a structure identical to that of group B meningococcus, which is non-immunogenic and shares common antigens with the brain. Another possible target may be the lipopolysaccharide (LPS). However there are a large number of different LPS serotypes that are shared

by various subgroups.

[0012] The inventors have found that components coded by the B2/D genome, but absent from A and B1 *E. coli* strains, are useful as antigens and can specifically prevent the pathologies due to ExPEC strains. It has also been found that homologous antigenic components coded by other pathogenic strains are useful to prevent the pathologies caused by such strains. Accordingly, any reference to products specific to ExPEC strains, and their uses will encompass such strains.

[0013] It is then an object of the invention to provide isolated antigenic polypeptides and polynucleotides belonging to the core B2/D genome and not present in commensal *E. coli*.

[0014] Another object of the invention is to provide antibodies raised against such antigenic polypeptides.

[0015] It is still another object of the invention to provide vectors and host cells containing said polynucleotides.

[0016] Another object of the invention is to provide vaccine compositions specific to extra intestinal infections caused by ExPEC and pathologies caused by other pathogenic strains expressing antigenic polypeptides homologous to the ExPEC antigenic polypeptides.

[0017] The invention also relates to means for detecting and treating a development of *E. coli* in a human or animal compartment which is extra-intestinal (systemic and non-diarrhoeal infections, such as septicaemia, pyelonephritis, or meningitis in the newborn).

[0018] The isolated antigenic polypeptides of the invention are specific to B2/D *E. coli* strains and not present in A and B1 isolates of *E. coli*. They are encoded by genes belonging to the core B2/D genome and are not present in commensal *E. coli*.

[0019] They have a sequence selected in the group comprising the sequences SEQ ID N°11 to N°66 or homologous sequences with a minimum of 40% of identity with the whole sequences SEQ ID N°11 to N°66, respectively.

[0020] Said polypeptides are obtainable by a process comprising the steps of

- 1- selecting on the basis of sequence analysis those of the polypeptides which are either located in the outer membrane or secreted by the bacteria,
- 2- identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates,
- 3- purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in the B2/D isolates,
- 4- testing the polypeptides for immunogenicity using animals models.

[0021] By the term "conserved", it is meant, according to the invention, that the genes coding for the polypeptides are present with a frequency of at least 50% in B2/D isolates, preferably greater than 60%, more preferably greater than 80% and even more preferably greater than 85%, and in less than 40% in A/B isolates, preferably in less than 20%, more preferably in less than 15%.

[0022] The animal models used in step 4 are infected adult animals, eventually immunodepressed and as models for neonatal infections infant animals.

[0023] The adult animals particularly mice, are infected intraperitoneally, the endpoint being the animal death and/or bacteremia measurement.

[0024] The animals can be immunodepressed by injection, for example, of cyclophosphamide which induces a neutropenia. Such a model will validate the use of the antigen for prevention of *E. coli* sepsis in immunodepressed patients.

The second animal model is for example 2 to 3 day old infant mice.

[0025] The variants or fractionnal sequences conserving the B2/D properties and which are antigenic as defined in step 4 of the above process are also part of the invention. The term "variant" is herein intended to mean any sequence having insertions and/or deletions and/or substitutions with respect to the parent sequence. The term "fractional" is herein intended to mean any fragment of the parent sequence.

[0026] The invention also relates to isolated polynucleotides coding for a polypeptide such as above defined according to the universal genetic code and taking into account the degeneracy of this code. The term "polynucleotide" encompasses any nucleotidic sequence such as DNA, including cDNA, RNA, including mRNA.

[0027] Said polynucleotides have preferably sequences corresponding to SEQ ID N°67 to SEQ ID N°132.

[0028] The present application is also aimed towards any vector comprising at least one of said polynucleotides and also any cell transformed by genetic engineering, characterized in that it comprises, by transfection, at least one of said polynucleotides and/or at least one vector according to the invention, and/or in that said transformation induces the production by this cell of at least one polypeptide corresponding to a polynucleotide such as above-defined.

[0029] The invention also relates to a process for isolating and identifying antigenic polypeptides, therefore useful as vaccine for *E. coli*.

[0030] Such a process comprises the steps of

- 1- selecting on the basis of sequence analysis those of the polypeptides which are either located in the outer membrane or secreted by the bacteria,

- 2- identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates,
- 3- purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in B2/D isolates,
- 4- testing the polypeptides for immunogenicity using animals models.

5 [0031] The selected antigenic polypeptides, alone or in combination, are capable of inducing an antibody response for prevention of infections due to ExPEC strains regardless of the pathogenesis and the infection site (UTI, pyelonephritis, sepsis, bacteremia, neonatal meningitis).

[0032] Such polypeptides particularly have sequences SEQ ID N°1 to SEQ ID N°66 or correspond to homologous sequences.

10 [0033] The invention thus relates to vaccine compositions specific to *E. coli* extra-intestinal infections, comprising an effective amount of at least one antigenic polypeptide as above defined with a carrier, particularly at least one polypeptide of SEQ ID N°1 to SEQ ID N°66 and the homologous sequences.

[0034] Such vaccine compositions are particularly useful for preventing urinary system infections, pyelonephritis, sepsis, bacteremia, neonatal meningitis.

15 [0035] The vaccine compositions of the invention are indicated for

- immunodepressed patients, ideally before the start of the immunosuppressive therapy : patients suffering from cancer, leukaemia, transplant patients, patients receiving long-term steroids therapy. The *E. coli* vaccine could then be administered in association with a *Staphylococcus aureus* vaccine.
- 20 - patients before surgery where there is a high risk of *E. coli* infections (abdominal surgery)
- patients with recurrent UTI, especially after one episode of pyelonephritis. The prevention of neonatal infections will require vaccination of the mother, implying vaccination long before pregnancy to avoid potential problem. Ideally such a vaccine should be associated with a Group B *Streptococcus* polysaccharide vaccine in order to also prevent late onset neonatal infections. It should be pointed out that the induction of a level of antibodies against B2/D *E. coli* in pregnant women would also prevent UTI, which are always a risk in the context of a pregnancy.

[0036] The formulation and the dose of said vaccine compositions can be developed and adjusted by those skilled in the art as a function of the indication targeted, of the method of administration desired, and of the patient under consideration (age, weight).

30 [0037] These compositions comprises one or more physiologically inert vehicles, and in particular any excipient suitable for the formulation and/or for the method of administration desired.

[0038] The antibodies raised against the above-identified polypeptides are also part of the invention.

[0039] They are capable of binding to said polypeptides in physiological-type conditions (*in vivo* or mimicking *in vivo*) when administered to a human or animal organism, and ELISA-type conditions when said binding product is intended to be used in assays and methods *in vitro*. Such antibodies advantageously inhibit the extra-intestinal growth of ExPEC strains in human or animal.

40 [0040] The methods for manufacturing such antibodies using the polypeptides according to the invention are available to those skilled in the art. They are conventional methods which comprise, in particular, the immunization of animals such as rabbits and the harvesting of the serum produced, followed optionally by the purification of the serum obtained. A technique suitable for the production of monoclonal antibodies is that of Köhler and Milstein (Nature 1975, 256:495-497).

[0041] Said antibodies do not recognize the cells of the human or animal to which it is intended.

[0042] The antibodies or fragments thereof are advantageously humanized when intended for a human administration.

45 [0043] The present invention is also aimed towards the use, in an effective amount, of at least one of said polypeptides, antibodies or polynucleotides for the diagnosis of the presence or absence of undesirable extra-intestinal *E. coli*, and/or for the diagnosis of an extra-intestinal *E. coli* infection.

[0044] The detection of the presence or absence of such compounds can in particular be carried out by nucleotide hybridization, by PCR amplification or by detection of their polypeptide products. Detection of the presence of such compounds makes it possible to conclude that a B2/D *E. coli* strain is present.

50 [0045] The present application is also aimed towards any use of a polypeptide such as above defined for the manufacture of a composition, in particular of a pharmaceutical composition, intended to alleviate and/or to prevent and/or to treat an undesirable growth of *E. coli*, such as an *E. coli* infection, (for example systemic and non-diarrhoeal infections), the presence of extra-intestinal *E. coli* or a sanitary contamination.

55 [0046] The present invention is illustrated by the examples which follow and which are given in a non limiting capacity.

**Example 1:** Assay for the immunogenicity of a selected polypeptide from sequences 1-66.

. cloning expression and purification of the selected polypeptide.

5 [0047] The nucleic acid having SEQ ID N°95 encoding the polypeptide corresponding to SEQ ID N°28 was cloned without the signal sequence (coding the 16 first amino acid) in a prokaryotic expression vector according to classical methods for cloning. The recombinant plasmid was used to transform the *E. coli* strain BL21. Transformed cells containing the recombinant plasmid were selected in LB medium with 100µg/ml ampicillin. Individual clones are picked and grown in presence of IPTG 1mM to induce recombinant protein expression. Total protein content of the culture  
10 cells was extracted by cell lysis. Recombinant protein was purified by affinity columns.

. Test for immunogenicity in an animal model

15 [0048] Polypeptide preparation from SEQ ID N°28 was injected to Swiss mice to induce an antibody response as follows :

At d0 a first immunisation was done by injecting 20µg of the protein at in 100µg solution of PBS and complet Freund adjuvant (1:1). Control animals were injected with 100µl solution of PBS and complet Freund adjuvant (1:1).  
Boosting injection at d21 with 10µg of protein in 100µl PBS and complet Freund adjuvant (1:1).

20 [0049] - Sera from vaccinated animals was prepared from blood drawn by puncture in the tail of the mice.  
[0050] Detection of specific antibodies in animal sera, at d20 before the boosting injection, was performed by western blot according to standart protocol. Purified polypeptide was subjected to electrophoresis (10µg per lane) and transfert to nitrocellulose membrane.

25 [0051] The membranes were then saturated by incubation 35 min with PBS/Tween20 0.1%/powder milk 5%.  
[0052] Diluted sera was incubated with the membrane for 45 min. Membranes were washed three time 5 min with PBS/tween. Bound antibodies were then recognized by an anti-mouse IgG coupled to horseradish peroxidase enzyme. After washing 3 times with PBS/Tween and 3 time with PBS, enzymatic activity was revealed by addition of chromogenic substrate DAB and hydrogen peroxyde.

30 [0053] Results : Sera from vaccinated animal, diluted at 1/100 revealed a unique band corresponding to the injected polypeptide. No antibody to the polypeptide could be detected in sera from control animals.

[0054] At d42, 300 µl of cyclophosphamide and 200µl at d45 were injected IP in the mice to induce neutropenia in order to increase the susceptibility to the challenge infection.

35 At d46 vaccinated and control mice were challenged by intraperitoneal injection of the wt B2/D strain C5 of *E. coli* at a dose equal to 10 time the LD50 (letal dose).

[0055] - Immunogenicity of the selected polypeptide and protection conferred by vaccination with the seleted polypeptide was assessed by the survival of vaccinated animals three days post challenge.

**Example 2 :** Vaccines compositions intending for prevention of any form of infection by ExPEC.

40 [0056] The polypeptide coded by a sequence comprising SEQ ID N°28 is conjugated with a toxin and added to a physiologically inert vehicle.

[0057] This conjugated peptide is optionnally added to a childhood vaccine.

[0058] The composition is sterilized and can be injected parenterally, subcutaneously or intramuscularly.

45 [0059] Said composition can also be sprayed onto mucosa with the aid of a spray.

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## SEQUENCE LISTING

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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**EP 1 342 784 A1**

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EP 1 342 784 A1

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 Asn Ala Ser Leu Thr Met Gln Gly His Ala Thr Glu His Ala Ile Phe  
 565 570 575  
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 Arg Ser Ser Ala Asn His Cys Ser Leu Val Phe Leu Cys Gly Thr Asp  
 580 585 590  
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 Trp Val Thr Val Leu Lys Glu Thr Glu Ser Ser Tyr Asn Lys Lys Phe  
 595 600 605  
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EP 1 342 784 A1

Asn Ser Asp Tyr Lys Ser Asn Asn Gln Gln Thr Ser Phe Asp Gln Pro  
610 615 620

5 Asp Trp Lys Thr Gly Val Phe Lys Phe Asp Thr Leu His Leu Asn Asn  
625 630 635 640

10 Ala Asp Phe Ser Ile Ser Arg Asn Ala Asn Val Glu Gly Asn Ile Ser  
645 650 655

15 Ala Asn Lys Ser Ala Ile Thr Ile Gly Asp Lys Asn Val Tyr Ile Asp  
660 665 670

Asn Leu Ala Gly Lys Asn Ile Thr Asn Asn Gly Phe Asp Phe Lys Gln  
675 680 685

20 Thr Ile Ser Thr Asn Leu Ser Ile Gly Glu Thr Lys Phe Thr Gly Gly  
690 695 700

25 Ile Thr Ala His Asn Ser Gln Ile Ala Ile Gly Asp Gln Ala Val Val  
705 710 715 720

Thr Leu Asn Gly Ala Thr Phe Leu Asp Asn Thr Pro Ile Ser Ile Asp  
725 730 735

30 Lys Gly Ala Lys Val Ile Ala Gln Asn Ser Met Phe Thr Thr Lys Gly  
740 745 750

35 Ile Asp Ile Ser Gly Glu Leu Thr Met Met Gly Ile Pro Glu Gln Asn  
755 760 765

40 Ser Lys Thr Val Thr Pro Gly Leu His Tyr Ala Ala Asp Gly Phe Arg  
770 775 780

45 Leu Ser Gly Gly Asn Ala Asn Phe Ile Ala Arg Asn Met Ala Ser Val  
785 790 795 800

Thr Gly Asn Ile Tyr Ala Asp Asp Ala Ala Thr Ile Thr Leu Gly Gln  
805 810 815

50 Pro Glu Thr Glu Thr Pro Thr Ile Ser Ser Ala Tyr Gln Ala Trp Ala  
820 825 830

55 Glu Thr Leu Leu Tyr Gly Phe Asp Thr Ala Tyr Arg Gly Ala Ile Thr

# EP 1 342 784 A1

	835	840	845
5	Ala Pro Lys Ala Thr Val Ser Met Asn Asn Ala Ile Trp His Leu Asn 850 855 860		
10	Ser Gln Ser Ser Ile Asn Arg Leu Glu Thr Lys Asp Ser Met Val Arg 865 870 875 880		
15	Phe Thr Gly Asp Asn Gly Lys Phe Thr Thr Leu Thr Val Asn Asn Leu 885 890 895		
20	Thr Ile Asp Asp Ser Ala Phe Val Leu Arg Ala Asn Leu Ala Gln Ala 900 905 910		
25	Asp Gln Leu Val Val Asn Lys Ser Leu Ser Gly Lys Asn Asn Leu Leu 915 920 925		
30	Leu Val Asp Phe Ile Glu Lys Asn Gly Asn Ser Asn Gly Leu Asn Ile 930 935 940		
35	Asp Leu Val Ser Ala Pro Lys Gly Thr Ala Val Asp Val Phe Lys Ala 945 950 955 960		
40	Thr Thr Arg Ser Ile Gly Phe Ser Asp Val Thr Pro Val Ile Glu Gln 965 970 975		
45	Lys Asn Asp Thr Asp Lys Ala Thr Trp Thr Leu Ile Gly Tyr Lys Ser 980 985 990		
50	Val Ala Asn Ala Asp Ala Ala Lys Lys Ala Thr Leu Leu Met Ser Gly 995 1000 1005		
55	Gly Tyr Lys Ala Phe Leu Ala Glu Val Asn Asn Leu Asn Lys Arg 1010 1015 1020		
	Met Gly Asp Leu Arg Asp Ile Asn Gly Glu Ser Gly Ala Trp Ala 1025 1030 1035		
	Arg Ile Ile Ser Gly Thr Gly Ser Ala Gly Gly Gly Phe Ser Asp 1040 1045 1050		
	Asn Tyr Thr His Val Gln Val Gly Ala Asp Asn Lys His Glu Leu 1055 1060 1065		



EP 1 342 784 A1

5 Asp Gly Leu Asp Leu Phe Thr Gly Val Thr Met Thr Tyr Thr Asp  
1070 1075 1080

10 Ser His Ala Gly Ser Asp Ala Phe Ser Gly Glu Thr Lys Ser Val  
1085 1090 1095

15 Gly Ala Gly Leu Tyr Ala Ser Ala Met Phe Glu Ser Gly Ala Tyr  
1100 1105 1110

20 Ile Asp Leu Ile Gly Lys Tyr Val His His Asp Asn Glu Tyr Thr  
1115 1120 1125

25 Ala Thr Phe Ala Gly Leu Gly Thr Arg Asp Tyr Ser Ser His Ser  
1130 1135 1140

30 Trp Tyr Ala Gly Ala Glu Val Gly Tyr Arg Tyr His Val Thr Asp  
1145 1150 1155

35 Ser Ala Trp Ile Glu Pro Gln Ala Glu Leu Val Tyr Gly Ala Val  
1160 1165 1170

40 Ser Gly Lys Gln Phe Ser Trp Lys Asp Gln Gly Met Asn Leu Thr  
1175 1180 1185

45 Met Lys Asp Lys Asp Phe Asn Pro Leu Ile Gly Arg Thr Gly Val  
1190 1195 1200

50 Asp Val Gly Lys Ser Phe Ser Gly Lys Asp Trp Lys Val Thr Ala  
1205 1210 1215

55 Arg Ala Gly Leu Gly Tyr Gln Phe Asp Leu Phe Ala Asn Gly Glu  
1220 1225 1230

Thr Val Leu Arg Asp Ala Ser Gly Glu Lys Arg Ile Lys Gly Glu  
1235 1240 1245

Lys Asp Gly Arg Met Leu Met Asn Val Gly Leu Asn Ala Glu Ile  
1250 1255 1260

Arg Asp Asn Leu Arg Phe Gly Leu Glu Phe Glu Lys Ser Ala Phe  
1265 1270 1275

EP 1 342 784 A1

Gly Lys Tyr Asn Val Asp Asn Ala Ile Asn Ala Asn Phe Arg Tyr  
1280 1285 1290

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Ser Phe  
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Met Ile Asn Ile Pro Ser Pro Thr Ala Val Val Met Ala Leu Val Ala  
1 5 10 15

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Ile Ser Thr Leu Pro Ser Pro Ser Arg Val Lys Leu Met Pro Tyr Pro  
20 25 30

Pro Arg Ala His Asn Thr Thr Gly Leu Leu Pro Val Arg Glu Ile Cys  
35 40 45

25

Phe Pro His His Gly Asp Asp Gly Arg Asn Ser Ile Glu Pro Ser Ile  
50 55 60

30

Ser Arg Ala Ala His Thr Asp Arg Leu Arg Phe Val Cys Met Thr Arg  
65 70 75 80

35

Thr Gly Ser Thr Thr Ser Arg Pro Phe Cys Pro Ile Pro Arg Ser Pro  
85 90 95

Ala Leu Asn Ala Ser Gly Gln Gln Asp Ser Gly Phe Trp Gly Val Ser  
100 105 110

40

Ser Ile Pro Gly Asp Ile Leu Met Phe Gln Leu His Val Leu Ile Val  
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Phe Ile Cys Lys Ile Asn Leu Ser Asp Asn Asn Ile Ser Tyr  
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EP 1 342 784 A1

Met Tyr Ala Arg Glu Tyr Arg Ser Thr Arg Pro His Lys Ala Ile Phe  
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5 Phe His Leu Ser Cys Leu Thr Leu Ile Cys Ser Ala Gln Val Tyr Ala  
20 25 30

10 Lys Pro Asp Met Arg Pro Leu Gly Pro Asn Ile Ala Asp Lys Gly Ser  
35 40 45

15 Val Phe Tyr His Phe Ser Ala Thr Ser Phe Asp Ser Val Asp Gly Thr  
50 55 60

Arg His Tyr Arg Val Trp Thr Ala Val Pro Asn Thr Thr Ala Pro Ala  
65 70 75 80

20 Ser Gly Tyr Pro Ile Leu Tyr Met Leu Asp Gly Asn Ala Val Met Asp  
85 90 95

25 Arg Leu Asp Asp Glu Leu Leu Lys Gln Leu Ser Glu Lys Thr Pro Pro  
100 105 110

30 Val Ile Val Ala Val Gly Tyr Gln Thr Asn Leu Pro Phe Asp Leu Asn  
115 120 125

Ser Arg Ala Tyr Asp Tyr Thr Pro Ala Ala Glu Ser Arg Lys Thr Asp  
130 135 140

35 Leu His Ser Gly Arg Phe Ser Arg Lys Ser Gly Gly Ser Asn Asn Phe  
145 150 155 160

40 Arg Gln Leu Leu Glu Thr Arg Ile Ala Pro Lys Val Glu Gln Gly Leu  
165 170 175

Asn Ile Asp Arg Gln Arg Arg Gly Leu Trp Gly His Ser Tyr Gly Gly  
180 185 190

45 Leu Phe Val Leu Asp Ser Trp Leu Ser Ser Ser Tyr Phe Arg Ser Tyr  
195 200 205

50 Tyr Ser Ala Ser Pro Ser Leu Gly Arg Gly Tyr Asp Ala Leu Leu Ser  
210 215 220

Arg Val Thr Ala Val Glu Pro Leu Gln Phe Cys Thr Lys His Leu Ala  
55

EP 1 342 784 A1

	225		230		235		240
5	Ile Met Glu Gly	Ser Ala Thr Gln Gly Asp Asn Arg Glu Thr His Ala	245		250		255
10	Val Gly Val Leu Ser Lys Ile His Thr Thr Leu Thr Ile Leu Lys Asp		260		265		270
15	Lys Gly Val Asn Ala Val Phe Trp Asp Phe Pro Asn Leu Gly His Gly		275		280		285
20	Pro Met Phe Asn Ala Ser Phe Arg Gln Ala Leu Leu Asp Ile Ser Gly		290		295		300
25	Glu Asn Ala Asn Tyr Thr Ala Gly Cys His Glu Leu Ser His		305		310		315
	<210>	8					
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35	Leu Asn Ser Gln Val Ser Val Ala Lys Tyr Ser Asp Asp Asp Asn Asp		20		25		30
40	Glu Thr Leu Val Val Glu Ala Thr Ala Glu Gln Val Leu Lys Gln Gln		35		40		45
45	Pro Gly Val Ser Val Ile Thr Ser Glu Asp Ile Lys Lys Thr Pro Pro		50		55		60
50	Val Asn Asp Leu Ser Asp Ile Ile Arg Lys Met Pro Gly Val Asn Leu		65		70		75
55	Thr Gly Asn Ser Ala Ser Gly Thr Arg Gly Asn Asn Arg Gln Ile Asp		85		90		95
	Ile Arg Gly Met Gly Pro Glu Asn Thr Leu Ile Leu Ile Asp Gly Val		100		105		110

EP 1 342 784 A1

Pro Val Thr Ser Arg Asn Ser Val Arg Tyr Ser Trp Arg Gly Glu Arg  
115 120 125

5 Asp Thr Arg Gly Asp Thr Asn Trp Val Pro Pro Glu Gln Val Glu Arg  
130 135 140

10 Ile Glu Val Ile Arg Gly Pro Ala Ala Ala Arg Tyr Gly Ser Gly Ala  
145 150 155 160

Ala Gly Gly Val Val Asn Ile Ile Thr Lys Arg Pro Thr Asn Asp Trp  
165 170 175

15 His Gly Ser Leu Ser Leu Tyr Thr Asn Gln Pro Glu Ser Ser Glu Glu  
180 185 190

20 Gly Ala Thr Arg Arg Ala Asn Phe Ser Leu Ser Gly Pro Leu Ala Gly  
195 200 205

25 Asp Ala Leu Thr Thr Arg Leu Tyr Gly Asn Leu Asn Lys Thr Asp Ala  
210 215 220

Asp Ser Trp Asp Ile Asn Ser Pro Val Gly Thr Lys Asn Ala Ala Gly  
225 230 235 240

30 His Glu Gly Val Arg Asn Lys Asp Ile Asn Gly Val Val Ser Trp Lys  
245 250 255

35 Leu Asn Pro Gln Gln Ile Leu Asp Phe Glu Val Gly Tyr Ser Arg Gln  
260 265 270

Gly Asn Ile Tyr Ala Gly Asp Thr Gln Asn Ser Ser Ser Ser Ala Val  
275 280 285

40 Thr Glu Ser Leu Ala Lys Ser Gly Lys Glu Thr Asn Arg Leu Tyr Arg  
290 295 300

45 Gln Asn Tyr Gly Ile Thr His Asn Gly Ile Trp Asp Trp Gly Gln Ser  
305 310 315 320

50 Arg Phe Gly Val Tyr Tyr Glu Lys Thr Asn Asn Thr Arg Met Asn Glu  
325 330 335

Gly Leu Ser Gly Gly Gly Glu Gly Arg Ile Leu Ala Gly Glu Lys Phe

55

EP 1 342 784 A1

	340	345	350
5	Thr Thr Asn Arg Leu Ser Ser Trp Arg Thr Ser Gly Glu Leu Asn Ile 355 360 365		
10	Pro Leu Asn Val Met Val Asp Gln Thr Leu Thr Val Gly Ala Glu Trp 370 375 380		
15	Asn Arg Asp Lys Leu Asp Asp Pro Ser Ser Thr Ser Leu Thr Val Asn 385 390 395 400		
20	Asp Arg Asp Ile Ser Gly Ile Ser Gly Ser Ala Ala Asp Arg Ser Ser 405 410 415		
25	Lys Asn His Ser Gln Ile Ser Ala Leu Tyr Ile Glu Asp Asn Ile Glu 420 425 430		
30	Pro Val Pro Gly Thr Asn Ile Ile Pro Gly Leu Arg Phe Asp Tyr Leu 435 440 445		
35	Ser Asp Ser Gly Gly Asn Phe Ser Pro Ser Leu Asn Leu Ser Gln Glu 450 455 460		
40	Leu Gly Asp Tyr Phe Lys Val Lys Ala Gly Val Ala Arg Thr Phe Lys 465 470 475 480		
45	Ala Pro Asn Leu Tyr Gln Ser Ser Glu Gly Tyr Leu Leu Tyr Ser Lys 485 490 495		
50	Gly Asn Gly Cys Pro Lys Asp Ile Thr Ser Gly Gly Cys Tyr Leu Ile 500 505 510		
55	Gly Asn Lys Asp Leu Asp Pro Glu Ile Ser Val Asn Lys Glu Ile Gly 515 520 525		
	Leu Glu Phe Thr Trp Glu Asp Tyr His Ala Ser Val Thr Tyr Phe Arg 530 535 540		
	Asn Asp Tyr Gln Asn Lys Ile Val Ala Gly Asp Asn Val Ile Gly Gln 545 550 555 560		
	Thr Ala Ser Gly Ala Tyr Ile Leu Lys Trp Gln Asn Gly Gly Lys Ala 565 570 575		

EP 1 342 784 A1

5 Leu Val Asp Gly Ile Glu Ala Ser Met Ser Phe Pro Leu Val Lys Glu  
580 585 590

Arg Leu Asn Trp Asn Thr Asn Ala Thr Trp Met Ile Thr Ser Glu Gln  
595 600 605

10 Lys Asp Thr Gly Asn Pro Leu Ser Val Ile Pro Lys Tyr Thr Ile Asn  
610 615 620

15 Asn Ser Leu Asn Trp Thr Ile Thr Gln Ala Phe Ser Ala Ser Phe Asn  
625 630 635 640

20 Trp Thr Leu Tyr Gly Arg Gln Lys Pro Arg Thr His Ala Glu Thr Arg  
645 650 655

Ser Glu Asp Thr Gly Gly Leu Ser Gly Lys Glu Leu Gly Ala Tyr Ser  
660 665 670

25 Leu Val Gly Thr Asn Phe Asn Tyr Asp Ile Asn Lys Asn Leu Arg Leu  
675 680 685

30 Asn Val Gly Val Ser Asn Ile Leu Asn Lys Gln Ile Phe Arg Ser Ser  
690 695 700

Glu Gly Ala Asn Thr Tyr Asn Glu Pro Gly Arg Ala Tyr Tyr Ala Gly  
705 710 715 720

35 Val Thr Ala Ser Phe  
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45 Met Gly Asn Gln Trp Gln Gln Lys Tyr Leu Leu Glu Tyr Asn Glu Leu  
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50 Val Ser Asn Phe Pro Ser Pro Glu Arg Val Val Ser Asp Tyr Ile Lys  
20 25 30

55 Asn Cys Phe Lys Thr Asp Leu Pro Trp Phe Ser Arg Ile Asp Pro Asp

EP 1 342 784 A1

	35	40	45
5	Asn Ala Tyr Phe Ile Cys Phe Ser Gln Asn Arg Ser Asn Ser Arg Ser	50	55 60
10	Tyr Thr Gly Trp Asp His Leu Gly Lys Tyr Lys Thr Glu Val Leu Thr	65	70 75 80
15	Leu Thr Gln Ala Ala Leu Ile Asn Ile Gly Tyr Arg Phe Asp Val Phe	85	90 95
20	Asp Asp Ala Asn Ser Ser Thr Gly Ile Tyr Lys Thr Lys Ser Ala Asp	100	105 110
25	Val Phe Asn Glu Glu Asn Glu Glu Lys Met Leu Pro Ser Glu Tyr Leu	115	120 125
30	His Phe Leu Gln Lys Cys Asp Phe Ala Gly Val Tyr Gly Lys Thr Leu	130	135 140
35	Ser Asp Tyr Trp Ser Lys Tyr Tyr Asp Lys Phe Lys Leu Leu Leu Lys	145	150 155 160
40	Asn Tyr Tyr Ile Ser Ser Ala Leu Tyr Leu Tyr Lys Asn Gly Glu Leu	165	170 175
45	Asp Glu Arg Glu Tyr Asn Phe Ser Met Asn Ala Leu Asn Arg Ser Asp	180	185 190
50	Asn Ile Ser Leu Leu Phe Phe Asp Ile Tyr Gly Tyr Tyr Ala Ser Asp	195	200 205
55	Ile Phe Val Ala Lys Asn Asn Asp Lys Val Met Leu Phe Ile Pro Gly	210	215 220
	Ala Lys Lys Pro Phe Leu Phe Lys Lys Asn Ile Ala Asp Leu Arg Leu	225	230 235 240
	Thr Leu Lys Glu Leu Ile Lys Asp Ser Asp Asn Lys Gln Leu Leu Ser	245	250 255
	Gln His Phe Ser Leu Tyr Ser Arg Gln Asp Gly Val Ser Tyr Ala Gly	260	265 270



EP 1 342 784 A1

5 Val Asn Ser Val Leu His Ala Ile Glu Asn Asp Gly Asn Phe Asn Glu  
275 280 285

10 Ser Tyr Phe Leu Tyr Ser Asn Lys Thr Leu Ser Asn Lys Asp Val Phe  
290 295 300

15 Asp Ala Ile Ala Ile Ser Val Lys Lys Arg Ser Phe Ser Asp Gly Asp  
305 310 315 320

20 Ile Val Ile Lys Ser Asn Ser Glu Ala Gln Arg Asp Tyr Ala Leu Thr  
325 330 335

Ile Leu Gln Thr Ile Leu Ser Met Thr Pro Ile Phe Asp Ile Val Val  
340 345 350

25 Pro Glu Val Ser Val Pro Leu Gly Leu Gly Ile Ile Thr Ser Ser Met  
355 360 365

Gly Ile Ser Phe Asp Gln Leu Ile Asn Gly Asp Thr Tyr Glu Glu Arg  
370 375 380

30 Arg Ser Ala Ile Pro Gly Leu Ala Thr Asn Ala Val Leu Leu Gly Leu  
385 390 395 400

35 Ser Phe Ala Ile Pro Leu Leu Ile Ser Lys Ala Gly Ile Asn Gln Glu  
405 410 415

Val Leu Ser Ser Val Ile Asn Asn Glu Gly Arg Thr Leu Asn Glu Thr  
420 425 430

40 Asn Ile Asp Ile Phe Leu Lys Glu Tyr Gly Ile Ala Glu Asp Ser Ile  
435 440 445

45 Ser Ser Thr Asn Leu Leu Asp Val Lys Leu Lys Ser Ser Gly Gln His  
450 455 460

50 Val Asn Ile Val Lys Leu Ser Asp Glu Asp Asn Gln Ile Val Ala Val  
465 470 475 480

Lys Gly Ser Ser Leu Ser Gly Ile Tyr Tyr Glu Val Asp Ile Glu Thr  
485 490 495

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EP 1 342 784 A1

Gly Tyr Glu Ile Leu Ser Arg Arg Ile Tyr Arg Thr Glu Tyr Asn Asn  
 500 505 510  
 5  
 Glu Ile Leu Trp Thr Arg Gly Gly Gly Leu Lys Gly Gly Gln Pro Phe  
 515 520 525  
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 Asp Phe Glu Ser Leu Asn Ile Pro Val Phe Phe Lys Asp Glu Pro Tyr  
 530 535 540  
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 Ser Ala Val Thr Gly Ser Pro Leu Ser Phe Ile Asn Asp Asp Ser Ser  
 545 550 555 560  
 Leu Leu Tyr Pro Asp Thr Asn Pro Lys Leu Pro Gln Pro Thr Ser Glu  
 565 570 575  
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 Met Asp Ile Val Asn Tyr Val Lys Gly Ser Gly Ser Phe Gly Asp Arg  
 580 585 590  
 25  
 Phe Val Thr Leu Met Arg Gly Ala Thr Glu Glu Glu Ala Trp Asn Ile  
 595 600 605  
 Ala Ser Tyr His Thr Ala Gly Gly Ser Thr Glu Glu Leu His Glu Ile  
 610 615 620  
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 Leu Leu Gly Gln Gly Pro Gln Ser Ser Leu Gly Phe Thr Glu Tyr Thr  
 625 630 635 640  
 35  
 Ser Asn Val Asn Ser Ala Asp Ala Ala Ser Arg Arg His Phe Leu Val  
 645 650 655  
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 Val Ile Lys Val His Val Lys Tyr Ile Thr Asn Asn Asn Val Ser Tyr  
 660 665 670  
 Val Asn His Trp Ala Ile Pro Asp Glu Ala Pro Val Glu Val Leu Ala  
 675 680 685  
 45  
 Val Val Asp Arg Arg Phe Asn Phe Pro Glu Pro Ser Thr Pro Pro Asp  
 690 695 700  
 50  
 Ile Ser Thr Ile Arg Lys Leu Leu Ser Leu Arg Tyr Phe Lys Glu Ser  
 705 710 715 720  
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EP 1 342 784 A1

Ile Glu Ser Thr Ser Lys Ser Asn Phe Gln Lys Leu Ser Arg Gly Asn  
725 730 735

5 Ile Asp Val Leu Lys Gly Arg Gly Ser Ile Ser Ser Thr Arg Gln Arg  
740 745 750

10 Ala Ile Tyr Pro Tyr Phe Glu Ala Ala Asn Ala Asp Glu Gln Gln Pro  
755 760 765

15 Leu Phe Phe Tyr Ile Lys Lys Asp Arg Phe Asp Asn His Gly Tyr Asp  
770 775 780

Gln Tyr Phe Tyr Asp Asn Thr Val Gly Leu Asn Gly Ile Pro Thr Leu  
785 790 795 800

20 Asn Thr Tyr Thr Gly Glu Ile Pro Ser Asp Ser Ser Ser Leu Gly Ser  
805 810 815

25 Thr Tyr Trp Lys Lys Tyr Asn Leu Thr Asn Glu Thr Ser Ile Ile Arg  
820 825 830

30 Val Ser Asn Ser Ala Arg Gly Ala Asn Gly Ile Lys Ile Ala Leu Glu  
835 840 845

Glu Val Gln Glu Gly Lys Pro Val Ile Ile Thr Ser Gly Asn Leu Ser  
850 855 860

35 Gly Cys Thr Thr Ile Val Ala Arg Lys Glu Gly Tyr Ile Tyr Lys Val  
865 870 875 880

40 His Thr Gly Thr Thr Lys Ser Leu Ala Gly Phe Thr Ser Thr Thr Gly  
885 890 895

45 Val Lys Lys Ala Val Glu Val Leu Glu Leu Leu Thr Lys Glu Pro Ile  
900 905 910

Pro Arg Val Glu Gly Ile Met Ser Asn Asp Phe Leu Val Asp Tyr Leu  
915 920 925

50 Ser Glu Asn Phe Glu Asp Ser Leu Ile Thr Tyr Ser Ser Ser Glu Lys  
930 935 940

55 Lys Pro Asp Ser Gln Ile Thr Ile Ile Arg Asp Asn Val Ser Val Phe

# EP 1 342 784 A1

945 950 955 960

5 Pro Tyr Phe Leu Asp Asn Ile Pro Glu His Gly Phe Gly Thr Ser Ala  
965 970 975

10 Thr Val Leu Val Arg Val Asp Gly Asn Val Val Val Arg Ser Leu Ser  
980 985 990

15 Glu Ser Tyr Ser Leu Asn Ala Asp Ala Ser Glu Ile Ser Val Leu Lys  
995 1000 1005

20 Val Phe Ser Lys Lys Phe  
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30 Gln Thr Asp Val Leu Val Ile Gly Gly Gly Pro Ala Gly Leu Ser Ala  
20 25 30

35 Ala Ile Ala Ala Gly Arg Leu Gly Ala Arg Thr Met Ile Val Glu Arg  
35 40 45

40 Tyr Gly Ser Leu Gly Gly Val Leu Thr Gln Val Gly Val Glu Ser Phe  
50 55 60

45 Ala Trp Tyr Arg His Pro Gly Thr Glu Asp Cys Glu Gly Ile Cys Arg  
65 70 75 80

Glu Tyr Glu Gly Arg Ala Arg Ala Leu Gly Phe Thr Arg Pro Glu Pro  
85 90 95

50 Gln Ser Ile Ser Glu Val Ile Asp Thr Glu Gly Phe Lys Val Val Ala  
100 105 110

55 Asp Gln Met Ile Thr Glu Ser Gly Val Glu Pro Leu Tyr His Ser Trp  
115 120 125

EP 1 342 784 A1

Val Val Asp Val Ile Lys Asp Gly Asp Thr Leu Cys Gly Val Ile Val  
130 135 140

5 Glu Asn Lys Ser Gly Arg Gly Ala Ile Leu Ala Lys Arg Ile Val Asp  
145 150 155 160

10 Cys Thr Gly Asp Ala Asp Ile Ala Ala Arg Ala Gly Ala Pro Trp Thr  
165 170 175

15 Lys Arg Ser Lys Asp Gln Leu Met Gly Val Thr Val Met Phe Ser Cys  
180 185 190

Ala Gly Val Asp Val Ala Arg Phe Asn Arg Phe Val Ala Glu Glu Leu  
195 200 205

20 Lys Pro Thr Tyr Ala Asp Trp Gly Lys Asn Trp Thr Ile Gln Thr Thr  
210 215 220

25 Gly Lys Glu Asp Pro Met Phe Ser Pro Tyr Met Glu Asp Ile Phe Thr  
225 230 235 240

Arg Ala Gln Gln Asp Gly Val Ile Pro Gly Asp Ala Gln Ala Ile Ala  
245 250 255

30 Gly Thr Trp Ser Thr Phe Ser Glu Ser Gly Glu Ala Phe Gln Met Asn  
260 265 270

35 Met Val Tyr Ala Phe Gly Phe Asp Cys Thr Asp Val Phe Asp Leu Thr  
275 280 285

40 Lys Ala Glu Ile Ala Gly Arg Gln Gln Ala Leu Trp Ala Ile Asp Ala  
290 295 300

Leu Arg His Tyr Val Pro Gly Phe Glu Asn Val Arg Leu Arg Asn Phe  
305 310 315 320

45 Gly Ala Thr Leu Gly Thr Arg Glu Ser Arg Leu Ile Glu Gly Glu Ile  
325 330 335

50 Arg Ile Ala Asp Asp Tyr Val Leu Asn Gln Gly Arg Cys Ser Asp Ser  
340 345 350

Val Gly Ile Phe Pro Glu Phe Ile Asp Gly Ser Gly Tyr Leu Ile Leu

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EP 1 342 784 A1

355 360 365

5 Pro Thr Thr Gly Arg Phe Phe Gln Ile Pro Tyr Gly Cys Leu Val Pro  
370 375 380

Gln Lys Val Glu Asn Leu Leu Val Ala Gly Arg Cys Ile Ser Ala Gly  
385 390 395 400

10 Val Val Ala His Thr Ser Met Arg Asn Met Met Cys Cys Ala Val Thr  
405 410 415

15 Gly Glu Ala Ala Gly Thr Ala Ala Val Val Ser Leu Gln Gln Asn Cys  
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20 Thr Val Arg Gln Val Ala Ile Pro Asp Leu Gln Asn Thr Leu Gln Gln  
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Gln Gly Val Arg Leu Ala  
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35 Ile Tyr His Phe Pro Ala Tyr Ser Ser Leu Glu Tyr Lys Gly Thr Phe  
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40 Gly Ser Ile Asn Ala Gly Tyr Ala Asp Trp Asn Ser Gly Phe Val Asn  
35 40 45

Thr His Arg Gly Glu Val Trp Lys Val Thr Ala Asp Phe Gly Val Asn  
50 55 60

45 Phe Lys Glu Ala Glu Phe Tyr Ser Phe Tyr Glu Ser Asn Val Leu Asn  
65 70 75 80

50 His Ala Val Ala Gly Arg Asn His Thr Val Ser Ala Met Thr His Val  
85 90 95

55

EP 1 342 784 A1

Arg Leu Phe Asp Ser Asp Met Thr Phe Phe Gly Lys Ile Tyr Gly Gln  
100 105 110

5 Trp Asp Asn Ser Trp Gly Asp Asp Leu Asp Met Phe Tyr Gly Phe Gly  
115 120 125

10 Tyr Leu Gly Trp Asn Gly Glu Trp Gly Phe Phe Lys Pro Tyr Ile Gly  
130 135 140

15 Leu His Asn Gln Ser Gly Asp Tyr Val Ser Ala Lys Tyr Gly Gln Thr  
145 150 155 160

Asn Gly Trp Asn Gly Tyr Val Val Gly Trp Thr Ala Val Leu Pro Phe  
165 170 175

20 Thr Leu Phe Asp Glu Lys Phe Val Leu Ser Asn Trp Asn Glu Ile Glu  
180 185 190

25 Leu Asp Arg Asn Asp Ala Tyr Thr Glu Gln Gln Phe Gly Arg Asn Gly  
195 200 205

Leu Asn Gly Gly Leu Thr Ile Ala Trp Lys Phe Tyr Pro Arg Trp Lys  
210 215 220

30 Ala Ser Val Thr Trp Arg Tyr Phe Asp Asn Lys Leu Gly Tyr Asp Gly  
225 230 235 240

35 Phe Gly Asp Gln Met Ile Tyr Met Leu Gly Tyr Asp Phe  
245 250

40 <210> 12  
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45 Met Ala Ser Leu Ile Gly Leu Ala Val Cys Thr Gly Asn Ala Phe Ser  
1 5 10 15

Pro Ala Leu Ala Ala Glu Ala Lys Gln Pro Asn Leu Val Ile Ile Met  
20 25 30

50 Ala Asp Asp Leu Gly Tyr Gly Asp Leu Ala Thr Tyr Gly His Gln Ile  
35 40 45

55

EP 1 342 784 A1

Val Lys Thr Pro Asn Ile Asp Arg Leu Ala Gln Glu Gly Val Lys Phe  
50 55 60

5

Thr Asp Tyr Tyr Ala Pro Ala Pro Leu Ser Ser Pro Ser Arg Ala Gly  
65 70 75 80

10

Leu Leu Thr Gly Arg Met Pro Phe Arg Thr Gly Ile Arg Ser Trp Ile  
85 90 95

15

Pro Ser Gly Lys Asp Val Ala Leu Gly Arg Asn Glu Leu Thr Ile Ala  
100 105 110

20

Asn Leu Leu Lys Ala Gln Gly Tyr Asp Thr Ala Met Met Gly Lys Leu  
115 120 125

25

Met Gly Phe Asp Tyr Ser Leu Ala Asn Thr Ala Gly Phe Val Thr Asp  
145 150 155 160

30

Ala Thr Leu Asp Asn Ala Lys Glu Arg Pro Arg Tyr Gly Met Val Tyr  
165 170 175

35

Pro Thr Gly Trp Leu Arg Asn Gly Gln Pro Thr Pro Arg Ala Asp Lys  
180 185 190

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Met Ser Gly Glu Tyr Val Ser Ser Glu Val Val Asn Trp Leu Asp Asn  
195 200 205

45

Lys Lys Asp Ser Lys Pro Phe Phe Leu Tyr Val Ala Phe Thr Glu Val  
210 215 220

50

His Ser Pro Leu Ala Ser Pro Lys Lys Tyr Leu Asp Met Tyr Ser Gln  
225 230 235 240

55

Tyr Met Ser Ala Tyr Gln Lys Gln His Pro Asp Leu Phe Tyr Gly Asp  
245 250 255

Trp Ala Asp Lys Pro Trp Arg Gly Val Gly Glu Tyr Tyr Ala Asn Ile  
260 265 270



EP 1 342 784 A1

Ser Tyr Leu Asp Ala Gln Val Gly Lys Val Leu Asp Lys Ile Lys Ala  
275 280 285

5 Met Gly Glu Glu Asp Asn Thr Ile Val Ile Phe Thr Ser Asp Asn Gly  
290 295 300

10 Pro Val Thr Arg Glu Ala Arg Lys Val Tyr Glu Leu Asn Leu Ala Gly  
305 310 315 320

Glu Thr Asp Gly Leu Arg Gly Arg Lys Asp Asn Leu Trp Glu Gly Gly  
325 330 335

15 Ile Arg Val Pro Ala Ile Ile Lys Tyr Gly Lys His Leu Pro Gln Gly  
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20 Met Val Ser Asp Thr Pro Val Tyr Gly Leu Asp Trp Met Pro Thr Leu  
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25 Ala Lys Met Met Asn Phe Lys Leu Pro Thr Asp Arg Thr Phe Asp Gly  
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Glu Ser Leu Val Pro Val Leu Glu Gln Lys Ala Leu Lys Arg Glu Lys  
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30 Pro Leu Ile Phe Gly Ile Asp Met Pro Phe Gln Asp Asp Pro Thr Asp  
405 410 415

35 Glu Trp Ala Ile Arg Asp Gly Asp Trp Lys Met Ile Ile Asp Arg Asn  
420 425 430

40 Asn Lys Pro Lys Tyr Leu Tyr Asn Leu Lys Ser Asp Arg Tyr Glu Thr  
435 440 445

Leu Asn Leu Ile Gly Lys Lys Pro Asp Ile Glu Lys Gln Met Tyr Gly  
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EP 1 342 784 A1

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 Ala Pro Ala Ile Phe Ala Ala Gln Val Ala Lys Leu Ser His Arg Ala  
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 Glu Arg Leu Arg His Glu Gly Val Ile Thr Asp Gly Ile His Val Met  
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 Thr Ala Glu His Ile Asp Lys Asp Leu Leu Lys Gln Cys Asn His Leu  
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 Arg Lys Ala Ile Thr Thr Ile Lys Ser Ala Gly Gly Thr Val Ser Phe  
 180 185 190

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 Asp Pro Asn Ile Arg Lys Glu Met Leu Ser Ile Pro Glu Met Ala Gln  
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EP 1342 784 A1

Ala Leu Asp Tyr Leu Ile Glu Tyr Thr Asp Ile Phe Ile Pro Ser Glu  
210 215 220

5 Ser Glu Leu Pro Phe Phe Ala Arg His Lys Asn Leu Ser Glu Glu Gln  
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10 Ile Val Ser Asp Leu Leu His Gly Gly Val Lys His Val Ala Ile Lys  
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Arg Ala Gln Arg Gly Ala Ser Tyr Tyr Lys Leu Lys Asn Gly Thr Leu  
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15 His Ala Gln His Val Ala Gly His Asp Ile Glu Ile Ile Asp Pro Thr  
275 280 285

20 Gly Ala Gly Asp Cys Phe Gly Ala Thr Phe Ile Thr Leu Phe Leu Ser  
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25 Gly Phe Pro Ala His Lys Ala Leu Gln Tyr Ala Asn Ala Ser Gly Ala  
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Ile Ser Thr Asn Ser Phe Ala Asp Asp Ile Thr His Ala Gly Val Val  
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50 Arg Ile Glu Gly Leu Ile Thr Glu Lys Thr Cys Ile Ile Ser Asp Glu  
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EP 1 342 784 A1

Ser Lys Asn Phe Thr Val Asn Met Pro Asp Val Pro Ser Ser Ser Val  
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 Arg Ser Ala Gly Asp Val Thr Glu Lys Val Tyr Phe Ser Ile Thr Leu  
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 Thr Arg Cys Gly Ser Asp Val Gly Asn Ala Tyr Ile Lys Phe Thr Gly  
 100 105 110  
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 Asn Thr Val Ser Glu Asp Ala Ser Leu Tyr Lys Leu Glu Asp Gly Ser  
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 Val Glu Gly Leu Ala Leu Thr Ile Phe Asp Lys Asn Lys Gly Ser Ile  
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 Ser Asn Asp Val Lys Ser Met Val Phe Ser Leu Thr Ser Ser Val Asp  
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 Asn Ile Leu His Phe Phe Ala Ala Tyr Lys Ala Leu Lys Asn Asn Val  
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 Ile Phe Thr Leu Thr Phe Leu Ala Glu Ile Ile Phe Ser Phe Pro Leu  
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# EP 1 342 784 A1

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 10 Tyr Ile Ser Pro Glu Lys Ser Ala Leu Leu Glu Asn Ile Arg Asn Phe  
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 15 Phe Leu Thr Phe Val Trp Leu Pro Leu Asn Phe Ser Pro Phe Trp Pro  
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 Gln Pro Trp Thr Asp Phe Val Gly Pro Ile Ser Ala Gln Leu Gly Phe  
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 20 Ala Leu Gly Tyr Tyr Cys Gln Trp Arg Ser Lys Asn Arg Ser His Arg  
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 45 Phe Gly Gly Ala Asp Thr Asp Trp Ser Thr Val Asp Tyr Pro Arg Leu  
 35 40 45  
 50 Thr Asp Met Asp Asp Asn Val Asp Ser Met Gly Gly Lys Ile Arg Phe  
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 Thr Gly Arg Val Val Lys Ala Thr Cys Lys Val Ala Thr Asp Ser Lys  
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EP 1 342 784 A1

65 70 75 80

5 Gln Ile Glu Val Val Leu Pro Val Val Pro Ser Asn Leu Phe Thr Gly  
85 90 95

10 Ile Asp Val Glu Ala Gln Gly Ala Ser Asn Gln Thr Asp Phe Asn Ile  
100 105 110

15 Asn Leu Thr Glu Cys Ser Asn Thr Asp Asp Gln Lys Ile Glu Phe Arg  
115 120 125

20 Phe Thr Gly Thr Ala Asp Ser Ala Asn Lys Thr Leu Ala Asn Glu Val  
130 135 140

25 Glu Gly Ser Thr Asp Ala Asp Asn Ser Gly Asn Ala Gly Ala Thr Gly  
145 150 155 160

30 Val Gly Ile Arg Ile Tyr Ser Lys Gly Thr Thr Asn Asn Gly Leu Ile  
165 170 175

35 Asn Leu Asn Thr Thr Ala Ala Glu Gly Ser Ala Ser Thr Ala Ala Tyr  
180 185 190

40 Thr Ile Pro Gly Asn Ala Thr Thr His Asp Phe Ser Ala Ala Phe Thr  
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EP 1 342 784 A1

Gly Arg Glu Arg Ala Tyr Cys Tyr Pro Gly Ser Pro Ser Asn Asn Thr  
35 40 45

5 Thr Pro Ala Ser Phe Ser Tyr Asn Phe Gly Thr Ile Val Val Ser Asp  
50 55 60

10 Val Asn Lys Asn Ala Pro Gly Thr Val Leu Pro Ser Gln Ile Trp Lys  
65 70 75 80

15 Val Gly Thr Tyr Lys Ala Tyr Cys Asn Ser Leu Asp Asp Tyr Glu Ile  
85 90 95

20 Tyr Phe Ser Ala Val Ser Gly Ile Asp Pro Ser Gly Ala Ser Gly Asp  
100 105 110

25 His Gln Gly Ser Asp Val Phe Ile Pro Leu Thr His Glu Ile Ser Val  
115 120 125

30 Ser Thr His Ile Lys Leu Tyr Asn Gln Asn Gly Thr Met Thr Asp Lys  
130 135 140

Ile Val Pro Phe Glu Asn Tyr Asn Thr Asn Tyr Pro Gly Asp Arg Ser  
145 150 155 160

35 Lys Pro Ser Asn Trp Ala Ser Gly Thr Glu Gly Tyr Ile Lys Ile Arg  
165 170 175

Ile Asp Lys Lys Ile Ile Ser Asp Val Ser Leu Ser Asn Val Leu Leu  
180 185 190

40 Val Ser Leu Tyr Val Ser Gln Ile Pro Thr Glu His Gly Pro Ile Pro  
195 200 205

45 Val Phe Asn Ala Tyr Ile Gly Asn Leu Asn Ile Gln Val Pro Gln Gly  
210 215 220

Cys Thr Ile Asn Glu Gly Thr Ser Phe Thr Val Asn Met Pro Asp Val  
225 230 235 240

50 Trp Ala Ser Glu Leu Ser Arg Ala Gly Ala Gly Ala Lys Pro Ala Gly  
245 250 255

55 Val Thr Pro Val Ala Thr Thr Ile Pro Ile Asn Cys Thr Asn Lys Asp

# EP 1 342 784 A1

260 265 270

5 Thr Asp Ala Val Met Thr Leu Val Phe Asp Gly Asn Ile Ser Ala Thr  
275 280 285

10 Arg Asp Thr Asn Gly Lys Gln Ser Ile Ile Gln Ala Gln Asp Asn Pro  
290 295 300

15 Asp Val Gly Ile Met Ile Met Asp Ser Gln Gln Asn Ser Val Asp Leu  
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Ser Ile Ala Gly Met Arg Phe Asn Pro Ala Phe Leu Ser Gly Asp Thr  
35 40 45

35 Glu Ala Val Ala Asp Leu Ser Arg Phe Glu Lys Gly Met Thr Tyr Leu  
50 55 60

40 Pro Gly Ser Tyr Glu Val Glu Val Trp Val Asn Asp Ser Pro Leu Leu  
65 70 75 80

Ser Arg Thr Val Thr Phe Lys Ala Asp Asp Glu Asn Gln Leu Ile Pro  
85 90 95

45 Cys Leu Ser Leu Ala Asp Leu Leu Ser Leu Gly Ile Asn Lys Asn Ala  
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50 Leu Pro Glu Gln Ala Leu Ala Ser Ser Glu Asn Ser Cys Leu Asp Leu  
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EP 1 342.784 A1

Arg Ile Trp Phe Pro Asp Val His Tyr Met Pro Glu Leu Asp Ala Gln  
130 135 140

5 Arg Leu Lys Leu Thr Phe Pro Gln Ala Ile Ile Lys Arg Asp Ala Arg  
145 150 155 160

10 Gly Tyr Ile Pro Pro Glu Gln Trp Asp Asn Gly Ile Thr Ala Phe Leu  
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15 Leu Asn Tyr Asp Phe Ser Gly Asn Asn Asp Arg Gly Asp Tyr Ser Ser  
180 185 190

Asn Asn Tyr Tyr Leu Asn Leu Arg Ala Gly Ile Asn Ile Gly Ala Trp  
195 200 205

20 Arg Phe Arg Asp Tyr Ser Thr Trp Ser Arg Gly Ser Asn Ser Ala Gly  
210 215 220

25 Lys Leu Glu His Ile Ser Ser Thr Leu Gln Arg Val Ile Ile Pro Phe  
225 230 235 240

Arg Ser Glu Leu Thr Leu Gly Asp Thr Trp Ser Ser Ser Asp Val Phe  
245 250 255

30 Asp Ser Val Ser Ile Arg Gly Ile Lys Leu Glu Ser Asp Glu Asn Met  
260 265 270

35 Leu Pro Asp Ser Gln Ser Gly Phe Ala Pro Thr Val Arg Gly Ile Ala  
275 280 285

40 Lys Ser Arg Ala Gln Val Thr Ile Lys Gln Asn Gly Tyr Val Ile Tyr  
290 295 300

Gln Thr Tyr Met Pro Pro Gly Pro Phe Glu Ile Ser Asp Leu Asn Pro  
305 310 315 320

45 Thr Ser Ser Ala Gly Asp Leu Glu Val Thr Ile Lys Glu Ser Asp Asn  
325 330 335

50 Ser Glu Thr Val Tyr Thr Val Pro Tyr Ala Ala Val Pro Ile Leu Gln  
340 345 350

55 Arg Glu Gly His Leu Lys Tyr Ser Thr Thr Val Gly Gln Tyr Arg Ser

EP 1 342 784 A1

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5	Asn Ser Tyr Asn Gln Lys Ser Pro Tyr Val Phe Gln Gly Glu Leu Ile 370 375 380		
10	Trp Gly Leu Pro Trp Asp Ile Thr Ala Tyr Gly Gly Ala Gln Phe Ser 385 390 395 400		
15	Glu Asp Tyr Arg Ala Leu Ala Leu Gly Leu Gly Leu Asn Leu Gly Val 405 410 415		
20	Phe Gly Ala Thr Ser Phe Asp Val Thr Gln Ala Asn Ser Ser Leu Val 420 425 430		
25	Asp Gly Ser Lys His Gln Gly Gln Ser Tyr Arg Phe Leu Tyr Ser Lys 435 440 445		
30	Ser Leu Val Gln Thr Gly Thr Ala Phe His Ile Ile Gly Tyr Arg Tyr 450 455 460		
35	Ser Thr Gln Gly Phe Tyr Thr Leu Ser Asp Thr Thr Tyr Gln Gln Met 465 470 475 480		
40	Ser Gly Thr Val Val Asp Pro Lys Thr Leu Asp Asp Lys Asp Tyr Val 485 490 495		
45	Tyr Asn Trp Asn Asp Phe Tyr Asn Leu Arg Tyr Ser Lys Arg Gly Lys 500 505 510		
50	Phe Gln Ala Ser Val Ser Gln Pro Phe Gly Asn Tyr Gly Ser Met Tyr 515 520 525		
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	Leu Tyr Gln Val Gly Tyr Asn Thr Ser Ile Lys Gly Ile Tyr Leu Asn 545 550 555 560		
	Val Ala Trp Asn Tyr Ser Lys Ser Pro Gly Thr Asn Ala Asp Lys Ile 565 570 575		
	Val Ser Leu Asn Val Ser Leu Pro Ile Ser Asn Trp Leu Ser Ser Thr 580 585 590		

EP 1 342 784 A1

5 Asn Asp Gly Arg Ser Ser Ser Asn Ala Met Thr Ala Thr Tyr Gly Tyr  
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10 Ser Gln Asp Asn His Gly Gln Val Asn Gln Tyr Thr Gly Val Ser Gly  
610 615 620

15 Ala Asn Gln Asp Asn Ser Ser Ser Gly Ser Val Gly Val Asn Tyr Arg  
645 650 655

20 Gly Ala Tyr Gly Ser Leu Asn Ser Ala Tyr Ser Tyr Asp Asn Glu Gly  
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25 Asn Gln Gln Ile Asn Tyr Gly Ile Ser Gly Ala Leu Val Val His Glu  
675 680 685

30 Asn Gly Leu Thr Leu Ser Gln Pro Leu Gly Glu Thr Asn Val Leu Ile  
690 695 700

35 Lys Ala Pro Gly Ala Asn Asn Val Asp Val Gln Arg Gly Thr Gly Ile  
705 710 715 720

40 Ser Thr Asp Trp Arg Gly Tyr Ala Val Val Pro Tyr Ala Thr Glu Tyr  
725 730 735

45 Arg Arg Asn Asn Ile Ser Leu Asp Pro Met Ser Met Asn Met His Thr  
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50 Glu Leu Asp Ile Thr Ser Thr Glu Val Ile Pro Gly Lys Gly Ala Leu  
755 760 765

55 Val Arg Ala Glu Phe Ala Ala His Ile Gly Ile Arg Gly Leu Phe Thr  
770 775 780

Val Arg Tyr Arg Asn Lys Ser Val Pro Phe Gly Ala Thr Ala Ser Ala  
785 790 795 800

Gln Ile Lys Asn Ser Ser Gln Ile Thr Gly Ile Val Gly Asp Asn Gly  
805 810 815

EP 1 342 784 A1

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 Gln Leu Tyr Leu Ser Gly Leu Pro Leu Glu Gly Val Ile Asn Ile Gln  
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 Trp Gly Asp Gly Val Gln Gln Lys Cys Gln Ala Asn Tyr Lys Leu Pro  
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 Ile Pro Ile Ala Ser Asn Ala Ser Asp Ala Leu Asn Gln Pro Ser Ser  
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 Ser Leu Asn Asp Gly Val Glu Thr Phe Phe Ile Ser Cys Phe Asp Met  
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 Pro Gln Glu Thr Thr Thr Asp Met Asp Ala Cys Gln Arg Val Gln Leu  
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 Ala Gln Val Ser Trp Val Lys Asn Lys Tyr Ser Val Ala Ala Leu Asn  
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 Arg Leu Lys Gln Asp Asn Lys Asp Asp Pro Gln Arg Leu Gln Glu Leu  
                   85                  90                  95

55  
 Thr Ala Ser Phe Asn Ala Glu Ser Glu Ala Trp Thr Glu Leu Ile Glu  
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60  
 Lys Ala Ser Lys Ser Val Gln Val Asp Tyr Val Gly Gly Thr Ile Ala  
                   115                  120                  125

65  
 Gly Thr Ala Val Ala Ser Arg Gln Ile Gly Leu Leu Glu Leu Gln Ser  
                   130                  135                  140

70  
 His Asp Ile Trp Glu His Trp Leu Arg Ser Arg Gly Leu Asn Ser Ser  
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Ser Phe Ala Arg Thr Lys Val Gln Ile  
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Phe Ser Leu Leu Phe Ala Ala Pro Met Ile His Ala Thr Asp Ser Val  
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Thr Thr Lys Asp Gly Glu Thr Ile Thr Val Thr Ala Asp Ala Asn Thr  
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25

Ala Thr Glu Ala Thr Asp Gly Tyr Gln Pro Leu Ser Thr Ser Thr Ala  
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Thr Leu Thr Asp Met Pro Met Leu Asp Ile Pro Gln Val Val Asn Thr  
65 70 75 80

Val Ser Asp Gln Val Leu Glu Asn Gln Asn Ala Thr Thr Leu Asp Glu  
85 90 95

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Ala Leu Tyr Asn Val Ser Asn Val Val Gln Thr Asn Thr Leu Gly Gly  
100 105 110

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Thr Gln Asp Ala Phe Val Arg Arg Gly Phe Gly Ala Asn Arg Asp Gly  
115 120 125

Ser Ile Met Thr Asn Gly Leu Arg Thr Val Leu Pro Arg Ser Phe Asn  
130 135 140

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Ala Ala Thr Glu Arg Val Glu Val Leu Lys Gly Pro Ala Ser Thr Leu  
145 150 155 160

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Tyr Gly Ile Leu Asp Pro Gly Gly Leu Ile Asn Val Val Thr Lys Arg  
165 170 175

Pro Glu Lys Thr Phe His Gly Ser Val Ser Ala Thr Ser Ser Ser Phe

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EP 1 342 784 A1

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15	Arg Asn Phe Gly Lys Glu Arg Ser Thr Phe Ile Ala Pro Ser Leu Thr 225 230 235 240		
20	Trp Phe Gly Asp Asn Ala Thr Val Thr Met Leu Tyr Ser His Arg Asp 245 250 255		
25	Tyr Lys Thr Pro Phe Asp Arg Gly Thr Ile Phe Asp Leu Thr Thr Lys 260 265 270		
30	Gln Pro Val Asn Val Asp Arg Lys Ile Arg Phe Asp Glu Pro Phe Asn 275 280 285		
35	Ile Thr Asp Gly Gln Ser Asp Leu Ala Gln Leu Asn Ala Glu Tyr His 290 295 300		
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50	Gly Thr Leu Thr Arg Arg Val Asp Ala Thr Gln Gly Ser Thr Gln Arg 340 345 350		
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	Phe Tyr Asn Glu Ile Leu Gly Gly Val Ser Tyr Glu Tyr Tyr Asp Leu 370 375 380		
	Leu Arg Thr Asp Met Ile Arg Cys Lys Lys Ala Lys Asp Phe Asn Ile 385 390 395 400		
	Tyr Asn Pro Val Tyr Gly Asn Thr Ser Lys Cys Thr Thr Val Ser Ala 405 410 415		

EP 1 342.784 A1

5 Ser Asp Ser Asp Gln Thr Ile Lys Gln Glu Asn Tyr Ser Ala Tyr Ala  
420 425 430

10 Gln Asp Ala Leu Tyr Leu Thr Asp Asn Trp Ile Ala Val Ala Gly Ile  
435 440 445

15 Arg Tyr Gln Tyr Tyr Thr Gln Tyr Ala Gly Lys Gly Arg Pro Phe Asn  
450 455 460

20 Val Asn Thr Asp Ser Arg Asp Glu Gln Trp Thr Pro Lys Leu Gly Leu  
465 470 475 480

25 Val Tyr Lys Leu Thr Pro Ser Val Ser Leu Phe Ala Asn Tyr Ser Gln  
485 490 495

30 Thr Phe Met Pro Gln Ser Ser Ile Ala Ser Tyr Ile Gly Asp Leu Pro  
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35 Pro Glu Ser Ser Asn Ala Tyr Glu Val Gly Ala Lys Phe Glu Leu Phe  
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40 Asp Gly Ile Thr Ala Asp Ile Ala Leu Phe Asp Ile His Lys Arg Asn  
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45 Val Leu Tyr Thr Glu Ser Ile Gly Asp Glu Thr Ile Ala Lys Thr Ala  
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50 Gly Arg Val Arg Ser Arg Gly Val Glu Val Asp Leu Ala Gly Ala Leu  
565 570 575

55 Thr Glu Asn Ile Asn Ile Ile Ala Ser Tyr Gly Tyr Thr Asp Ala Lys  
580 585 590

60 Val Leu Glu Asp Pro Asp Tyr Ala Gly Lys Pro Leu Pro Asn Val Pro  
595 600 605

65 Arg His Thr Gly Ser Leu Phe Leu Thr Tyr Asp Ile His Asn Met Pro  
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70 Gly Asn Asn Thr Leu Thr Phe Gly Gly Gly Gly His Gly Val Ser Arg  
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# EP 1 342 784 A1

Arg Ser Ala Thr Asn Gly Ala Asp Tyr Tyr Leu Pro Gly Tyr Phe Val  
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 Ala Asp Ala Phe Ala Ala Tyr Lys Met Lys Leu Gln Tyr Pro Val Thr  
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 Leu Gln Leu Asn Val Lys Asn Leu Phe Asp Lys Thr Tyr Tyr Thr Ser  
 675 680 685  
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 Ser Ile Ala Thr Asn Asn Leu Gly Asn Gln Ile Gly Asp Pro Arg Glu  
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 Val Gln Phe Thr Val Lys Met Glu Phe  
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 Phe Leu His Leu Arg Phe Asn Thr Leu Ser Ser Thr Asp Lys Met Arg  
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 Leu Glu Met Tyr Lys Ser Thr Leu Tyr Ser Thr Ile Glu Gln Phe Tyr  
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 Val Leu Pro Tyr Met Leu Ser Thr Asp His Ile Ile Arg Gln Ala Val  
 65 70 75 80  
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 Ile Thr Pro Asp Asp Met Thr Ser Ser Glu Leu Asn Gln Arg Ile Ala  
 85 90 95  
 50  
 His Phe Asn Thr Gln Leu Lys Thr Ala Ala Ile Phe Ile Leu Asp Thr  
 100 105 110  
 Gln Gly Lys Ala Ile Ala Ser Ser Asn Trp Gln Asp Pro Gly Ser Tyr  
 115 120 125  
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EP 1 342 784 A1

5 Val Gly Gln Asn Tyr Ser Tyr Arg Pro Tyr Tyr Lys His Ala Met Ser  
130 135 140

Gly Leu Asn Gly Arg Phe Tyr Gly Ile Gly Ser Thr Thr Asn Thr Pro  
145 150 155 160

10 Gly Phe Phe Leu Ser Thr Ser Ile Lys Asp Lys Gly Lys Ile Val Gly  
165 170 175

15 Val Val Val Val Lys Ile Ser Leu Asn Glu Ile Glu Lys Ala Trp Ala  
180 185 190

Glu Gly Pro Glu Asn Ile Ile Val Asn Asp Glu His Gly Ile Ile Phe  
195 200 205

20 Leu Ser Ser Lys Ser Pro Trp Arg Met Arg Thr Leu Gln Pro Leu Pro  
210 215 220

25 Val Gln Ala Lys Gln Lys Leu Gln Ser Thr Arg Gln Tyr Ser Leu Asp  
225 230 235 240

30 Asn Leu Leu Pro Ala Asp Tyr Tyr Pro Cys Tyr Thr Val Ser Asn Phe  
245 250 255

Thr Phe Leu Lys Asp Lys Lys Glu Gln Leu Cys Leu Phe Pro Gln Tyr  
260 265 270

35 Tyr Thr Gln Gln Ile Ala Ile Pro Glu Phe Asn Trp Lys Met Thr Ile  
275 280 285

40 Met Val Pro Leu Asp Asn Leu Tyr Trp Ser Trp Ala Ile Ser Leu Val  
290 295 300

Ile Thr Leu Ile Ile Tyr Leu Leu Phe Leu Leu Phe Ile Lys Tyr Trp  
305 310 315 320

Arg Met Arg Ser His Ala Gln Gln Leu Leu Thr Leu Ala Asn Glu Thr  
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50 Leu Glu Lys Gln Val Lys Glu Arg Thr Ser Ala Leu Glu Leu Ile Asn  
340 345 350

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EP 1 342 784 A1

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 Gln Lys Leu Ile Gln Glu Ile Lys Glu Arg Ser Gln Ala Glu Gln Val  
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 Leu Gly Gln Met Ala Thr Glu Ile Ala His Glu Gln Asn Gln Pro Leu  
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 Ala Ala Ile His Ala Leu Thr Asp Asn Ala Arg Thr Met Leu Lys Lys  
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 Glu Met Tyr Pro Gln Val Glu Gln Asn Leu Lys His Ile Ile Ser Val  
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 Ile Glu Arg Met Thr Gln Leu Ile Ser Glu Leu Lys Ala Phe Ala Ser  
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 Arg His Arg Val Pro Lys Gly Ser Ala Asp Val Ile Lys Val Met Tyr  
 450 455 460

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 Ser Ala Val Ala Leu Leu Asn His Ser Met Glu Lys Asn Asn Ile Glu  
 465 470 475 480

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 Arg Arg Ile Lys Ala Pro Ser Met Pro Leu Phe Val Asn Cys Asp Glu  
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 Leu Gly Leu Glu Gln Ile Phe Ser Asn Leu Ile Ser Asn Ala Leu Asp  
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 Ser Met Glu Gly Ser Ser Tyr Lys Arg Leu Asp Ile Ala Ile Arg Gln  
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 Ala Asn Asn Lys Val Ile Ile Thr Ile Lys Asp Ser Gly Gly Gly Phe  
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 Ala Pro Glu Val Val Asp Arg Ile Phe Glu Pro Phe Phe Thr Thr Lys  
 545 550 555 560

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 Arg Arg Gly Met Gly Leu Gly Leu Ala Ile Val Ser Glu Ile Val Arg  
 565 570 575

EP 1 342 784 A1

Asn Ser Asn Gly Ala Leu His Ala Ser Asn His Pro Glu Gly Gly Ala  
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5 Val Met Thr Leu Thr Trp Pro Glu Trp Gly Glu Glu His Glu  
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20 Leu Thr Leu Leu Ser Gly Thr Val Met Ser Gln Met Pro Leu Tyr Phe  
20 25 30

25 Leu Asn Thr Gln Lys Lys Leu Thr Ala His Tyr Glu Trp Leu Gln Ile  
35 40 45

Asn Leu Thr Asp Thr Tyr Glu Leu Val Lys Arg Leu Met Pro Ile Pro  
50 55 60

30 Ser Leu Asp Val Val Val Lys Val Gly Lys Leu Val Leu Pro Glu Lys  
65 70 75 80

35 Gly His His Gly Phe Tyr Pro Glu Ala Gly Val Val Tyr Arg Thr Val  
85 90 95

Ala Pro Glu Asn Pro  
100

40 <210> 23  
<211> 263  
<212> PRT  
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45 <400> 23

Met Met Lys Asn Thr Gly Tyr Ile Leu Ala Leu Cys Leu Thr Ala Ser  
1 5 10 15

50 Gly His Val Leu Ala His Asp Val Trp Ile Thr Gly Lys Gln Ala Glu  
20 25 30

55 Asn Asn Val Thr Ala Glu Ile Gly Tyr Gly His Asn Phe Pro Ser Lys

EP 1 342 784 A1

	35	40	45
5	Gly Thr Ile Pro Asp Arg Arg Asp Phe Phe Glu Asn Pro Arg Leu Tyr		
	50	55	60
10	Asn Gly Lys Glu Thr Ile Thr Leu Lys Pro Ala Ser Thr Asp Tyr Val		
	65	70	75
	Tyr Lys Thr Glu Ser Ala Ser Lys Asp Asn Gly Tyr Val Leu Ser Thr		
		85	90
15	Tyr Met Lys Pro Gly Tyr Trp Ser Arg Thr Ser Ser Gly Trp Lys Pro		
		100	105
20	Val Ser Arg Glu Gly Arg Asn Asp Val Ala Tyr Cys Glu Phe Val Thr		
		115	120
	Lys Tyr Ala Lys Ser Phe Ile Pro Gly Glu Gln Gln Met Pro Ala Gln		
		130	135
25	Leu Tyr Gln Ser Pro Thr Gly His Glu Leu Glu Ile Ile Pro Leu Ser		
		145	150
30	Asp Ile Ser Arg Phe Ser Glu Asn Val Lys Leu Lys Val Leu Tyr Lys		
		165	170
35	Thr Ser Pro Leu Ala Gly Ala Ile Met Glu Leu Asp Ser Val Ser Tyr		
		180	185
	Leu Thr Ser Ser Arg His Thr His Ala Val Glu His Lys His Pro Val		
		195	200
40	His Lys Ala Glu Leu Thr Phe Val Thr Asn Glu Asp Gly Ile Val Thr		
		210	215
45	Val Pro Ser Leu His Ile Gly Gln Trp Leu Ala Lys Val Gln Asn Lys		
		225	230
	Lys Ser Phe Gln Asp Lys Ser Leu Cys Asp Glu Thr Val Asp Val Ala		
		245	250
50	Thr Leu Ser Phe Ser Arg Asn		
		260	
55			

EP 1 342 784 A1

5 <210> 24  
 <211> 378  
 <212> PRT  
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 <400> 24

10 Met Gly Lys Ile Lys Tyr Trp Leu Ile Val Gly Phe Ile Ile Leu Phe  
 1 5 10 15

15 Ala Ile Phe Tyr Ile Ala Ile Ser Asp Arg Asp Ser Thr Leu Ser Arg  
 20 25 30

20 Leu Lys Ser Ala Gly Glu Asn Gly Asp Val Glu Ala Gln Tyr Ala Leu  
 35 40 45

Gly Leu Met Tyr Leu Tyr Gly Glu Ile Leu Asp Val Asp Tyr Gln Gln  
 50 55 60

25 Ala Lys Ile Trp Tyr Glu Lys Ala Ala Asp Gln Asn Asp Pro Arg Ala  
 65 70 75 80

30 Gln Ala Lys Leu Gly Val Met Tyr Ala Asn Gly Leu Gly Val Asn Gln  
 85 90 95

Asp Tyr Gln Gln Ser Lys Leu Trp Tyr Glu Lys Ala Ala Ala Gln Asn  
 100 105 110

35 Asp Val Asp Ala Gln Phe Leu Leu Gly Glu Met Tyr Asp Asp Gly Leu  
 115 120 125

40 Gly Val Ser Gln Asp Tyr Gln His Ala Lys Met Trp Tyr Glu Lys Ala  
 130 135 140

45 Ala Ala Gln Asn Asp Glu Arg Ala Gln Val Asn Leu Ala Val Leu Tyr  
 145 150 155 160

Ala Lys Gly Asn Gly Val Glu Gln Asp Tyr Arg Gln Ala Lys Ser Trp  
 165 170 175

50 Tyr Glu Lys Ala Ala Ala Gln Asn Ser Pro Asp Ala Gln Phe Ala Leu  
 180 185 190

55 Gly Ile Leu Tyr Ala Asn Ala Asn Gly Val Glu Gln Asp Tyr Gln Gln

# EP 1 342 784 A1

	195	200	205
5	Ala Lys Asp Trp Tyr Glu Lys Ala Ala Glu Gln Asn Phe Ala Asn Ala 210 215 220		
10	Gln Phe Asn Leu Gly Met Leu Tyr Tyr Lys Gly Glu Gly Val Lys Gln 225 230 235 240		
15	Asn Phe Arg Gln Ala Arg Glu Trp Phe Glu Lys Ala Ala Ser Gln Asn 245 250 255		
20	Gln Pro Asn Ala Gln Tyr Asn Leu Gly Gln Ile Tyr Tyr Tyr Gly Gln 260 265 270		
25	Gly Val Thr Gln Ser Tyr Arg Gln Ala Lys Asp Trp Phe Glu Lys Ala 275 280 285		
30	Ala Glu Lys Gly His Val Asp Ala Gln Tyr Asn Leu Gly Val Ile Tyr 290 295 300		
35	Glu Asn Gly Glu Gly Val Ser Gln Asn Tyr Gln Gln Ala Lys Ala Trp 305 310 315 320		
40	Tyr Glu Lys Ala Ala Ser Gln Asn Asp Ala Gln Ala Gln Phe Glu Leu 325 330 335		
45	Gly Val Met Asn Glu Leu Gly Gln Gly Glu Ser Ile Asp Leu Lys Gln 340 345 350		
50	Ala Arg His Tyr Tyr Glu Arg Ser Cys Asn Asn Gly Leu Lys Lys Gly 355 360 365		
55	Cys Glu Arg Leu Lys Glu Leu Leu Tyr Lys 370 375		
	<210> 25 <211> 654 <212> PRT <213> Escherichia coli <400> 25		
	Met Asn Val Ile Arg Thr Val Ile Cys Thr Leu Ile Ile Leu Pro Val 1 5 10 15		

EP 1 342 784 A1

Gly Leu Gln Ala Ala Thr Ser His Ser Ser Met Val Lys Asp Thr Ile  
 20 25 30

5 Thr Ile Val Ala Thr Gly Asn Gln Asn Thr Val Phe Glu Thr Pro Ser  
 35 40 45

10 Met Val Ser Val Val Thr Asn Asp Thr Pro Trp Ser Gln Asn Ala Val  
 50 55 60

15 Thr Ser Ala Gly Met Leu Lys Gly Val Ala Gly Leu Ser Gln Thr Gly  
 65 70 75 80

Ala Gly Arg Thr Asn Gly Gln Thr Phe Asn Leu Arg Gly Tyr Asp Lys  
 85 90 95

20 Ser Gly Val Leu Val Leu Val Asp Gly Val Arg Gln Leu Ser Asp Met  
 100 105 110

25 Ala Lys Ser Ser Gly Thr Tyr Leu Asp Pro Ala Leu Val Lys Arg Ile  
 115 120 125

30 Glu Val Val Arg Gly Pro Asn Ser Ser Leu Tyr Gly Ser Gly Gly Leu  
 130 135 140

Gly Gly Val Val Asp Phe Arg Thr Ala Asp Ala Ala Asp Phe Leu Pro  
 145 150 155 160

35 Pro Gly Glu Thr Asn Gly Leu Ser Leu Trp Gly Asn Ile Ala Ser Gly  
 165 170 175

40 Asp His Ser Thr Gly Ser Gly Leu Thr Trp Phe Gly Lys Thr Gly Lys  
 180 185 190

45 Thr Asp Ala Leu Leu Ser Val Ile Met Arg Lys Arg Gly Asn Ile Tyr  
 195 200 205

Gln Ser Asp Gly Glu His Ala Pro Asn Lys Glu Lys Pro Ala Ala Leu  
 210 215 220

50 Phe Ala Lys Gly Ser Val Gly Ile Thr Asp Ser Asn Lys Ala Gly Ala  
 225 230 235 240

55 Ser Leu Arg Leu Tyr Arg Asn Asn Thr Thr Glu Pro Gly Asn Ser Thr

# EP 1 342 784 A1

		245		250		255
5	Gln Thr His Gly Asp Ser Gly Leu Arg Asp Arg Lys Thr Val Gln Asn	260		265		270
10	Asp Val Gln Phe Trp Tyr Gln Tyr Ala Pro Val Asp Asn Ser Leu Ile	275		280		285
15	Asn Val Lys Ser Thr Leu Tyr Leu Ser Asp Ile Thr Ile Lys Thr Asn	290		295		300
20	Gly His Asn Lys Thr Ala Glu Trp Arg Asn Asn Arg Thr Ser Gly Val	305		310		315
25	Asn Val Val Asn Arg Ser His Thr Leu Ile Phe Pro Gly Ala His Gln	325		330		335
30	Leu Ser Tyr Gly Ala Glu Tyr Tyr Arg Gln Gln Gln Lys Pro Glu Gly	340		345		350
35	Ser Ala Thr Leu Tyr Pro Glu Gly Asn Ile Asp Phe Thr Ser Leu Tyr	355		360		365
40	Phe Gln Asp Glu Met Thr Met Lys Ser Tyr Pro Val Asn Ile Ile Val	370		375		380
45	Gly Ser Arg Tyr Asp Arg Tyr Lys Ser Phe Asn Pro Arg Ala Gly Glu	385		390		395
50	Leu Lys Ala Glu Arg Leu Ser Pro Arg Ala Ala Ile Ser Val Ser Pro	405		410		415
55	Thr Asp Trp Leu Met Met Tyr Gly Ser Ile Ser Ser Ala Phe Arg Ala	420		425		430
	Pro Thr Met Ala Glu Met Tyr Arg Asp Asp Val His Phe Tyr Arg Lys	435		440		445
	Gly Lys Pro Asn Tyr Trp Val Pro Asn Leu Asn Leu Lys Pro Glu Asn	450		455		460
	Asn Ile Thr Arg Glu Ile Gly Ala Gly Ile Gln Leu Asp Gly Leu Leu	465		470		475
						480



EP 1 342 784 A1

5 Thr Asp Asn Asp Arg Leu Gln Leu Lys Gly Gly Tyr Phe Gly Thr Asp  
485 490 495

Ala Arg Asn Tyr Ile Ala Thr Arg Val Asp Met Lys Arg Met Arg Ser  
500 505 510

10 Tyr Ser Tyr Asn Val Ser Arg Ala Arg Ile Trp Gly Trp Asp Met Gln  
515 520 525

15 Gly Asn Tyr Gln Ser Asp Tyr Val Asp Trp Met Leu Ser Tyr Asn Arg  
530 535 540

20 Thr Glu Ser Met Asp Ala Ser Ser Arg Glu Trp Leu Gly Ser Gly Asn  
545 550 555 560

Pro Asp Thr Leu Ile Ser Asp Ile Ser Ile Pro Val Gly His Arg Gly  
565 570 575

25 Val Tyr Ala Gly Trp Arg Ala Glu Leu Ser Ala Ser Ala Thr His Val  
580 585 590

30 Lys Lys Gly Asp Pro His Gln Ala Gly Tyr Thr Ile His Ser Phe Ser  
595 600 605

35 Leu Ser Tyr Lys Pro Val Ser Val Lys Gly Phe Glu Ala Ser Val Thr  
610 615 620

Leu Asp Asn Ala Phe Asn Lys Leu Ala Met Asn Gly Lys Gly Val Pro  
625 630 635 640

40 Leu Ser Gly Arg Thr Val Ser Leu Tyr Thr Arg Tyr Gln Trp  
645 650

45 <210> 26  
<211> 1376  
<212> PRT  
<213> Escherichia coli  
<400> 26

50 Met Asn Lys Ile Tyr Ala Leu Lys Tyr Cys Tyr Ile Thr Asn Thr Val  
1 5 10 15

55 Lys Val Val Ser Glu Leu Ala Arg Arg Val Cys Lys Gly Ser Thr Arg

EP 1 342 784 A1

	20	25	30
5	Arg Gly Lys Arg Leu Ser Val	Leu Thr Ser Leu Ala Leu Ser Ala Leu	
	35	40	45
10	Leu Pro Thr Val Ala Gly Ala Ser Thr Val Gly Gly Asn Asn Pro Tyr		
	50	55	60
15	Gln Thr Tyr Arg Asp Phe Ala Glu Asn Lys Gly Gln Phe Gln Ala Gly		
	65	70	75 80
20	Ala Thr Asn Ile Pro Ile Phe Asn Asn Lys Gly Glu Leu Val Gly His		
	85	90	95
25	Leu Asp Lys Ala Pro Met Val Asp Phe Ser Ser Val Asn Val Ser Ser		
	100	105	110
30	Asn Pro Gly Val Ala Thr Leu Ile Asn Pro Gln Tyr Ile Ala Ser Val		
	115	120	125
35	Lys His Asn Lys Gly Tyr Gln Ser Val Ser Phe Gly Asp Gly Gln Asn		
	130	135	140
40	Ser Tyr His Ile Val Asp Arg Asn Glu His Ser Ser Ser Asp Leu His		
	145	150	155 160
45	Thr Pro Arg Leu Asp Lys Leu Val Thr Glu Val Ala Pro Ala Thr Val		
	165	170	175
50	Thr Ser Ser Ser Thr Ala Asp Ile Leu Asn Pro Ser Lys Tyr Ser Ala		
	180	185	190
55	Phe Tyr Arg Ala Gly Ser Gly Ser Gln Tyr Ile Gln Asp Ser Gln Gly		
	195	200	205
60	Lys Arg His Trp Val Thr Gly Gly Tyr Gly Tyr Leu Thr Gly Gly Ile		
	210	215	220
65	Leu Pro Thr Ser Phe Phe Tyr His Gly Ser Asp Gly Ile Gln Leu Tyr		
	225	230	235 240
70	Met Gly Gly Asn Ile His Asp His Ser Ile Leu Pro Ser Phe Gly Glu		
	245	250	255

EP 1 342 784 A1

5 Ala Gly Asp Ser Gly Ser Pro Leu Phe Gly Trp Asn Thr Ala Lys Gly  
260 265 270

Gln Trp Glu Leu Val Gly Val Tyr Ser Gly Val Gly Gly Gly Thr Asn  
275 280 285

10 Leu Ile Tyr Ser Leu Ile Pro Gln Ser Phe Leu Ser Gln Ile Tyr Ser  
290 295 300

15 Glu Asp Asn Asp Ala Pro Val Phe Phe Asn Ala Ser Ser Gly Ala Pro  
305 310 315 320

20 Leu Gln Trp Lys Phe Asp Ser Ser Thr Gly Thr Gly Ser Leu Lys Gln  
325 330 335

Gly Ser Asp Glu Tyr Ala Met His Gly Gln Lys Gly Ser Asp Leu Asn  
340 345 350

25 Ala Gly Lys Asn Leu Thr Phe Leu Gly His Asn Gly Gln Ile Asp Leu  
355 360 365

30 Glu Asn Ser Val Thr Gln Gly Ala Gly Ser Leu Thr Phe Thr Asp Asp  
370 375 380

Tyr Thr Val Thr Thr Ser Asn Gly Ser Thr Trp Thr Gly Ala Gly Ile  
385 390 395 400

35 Ile Val Asp Lys Asp Ala Ser Val Asn Trp Gln Val Asn Gly Val Lys  
405 410 415

40 Gly Asp Asn Leu His Lys Ile Gly Glu Gly Thr Leu Val Val Gln Gly  
420 425 430

45 Thr Gly Val Asn Glu Gly Gly Leu Lys Val Gly Asp Gly Thr Val Val  
435 440 445

Leu Asn Gln Gln Ala Asp Ser Ser Gly His Val Gln Ala Phe Ser Ser  
450 455 460

50 Val Asn Ile Ala Ser Gly Arg Pro Thr Val Val Leu Ala Asp Asn Gln  
465 470 475 480

55

EP 1 342 784 A1

5 Gln Val Asn Pro Asp Asn Ile Ser Trp Gly Tyr Arg Gly Gly Val Leu  
485 490 495

Asp Val Asn Gly Asn Asp Leu Thr Phe His Lys Leu Asn Ala Ala Asp  
500 505 510

10 Tyr Gly Ala Thr Leu Gly Asn Ser Ser Asp Lys Thr Ala Asn Ile Thr  
515 520 525

15 Leu Asp Tyr Gln Thr Arg Pro Ala Asp Val Lys Val Asn Glu Trp Ser  
530 535 540

Ser Ser Asn Arg Gly Thr Val Gly Ser Leu Tyr Ile Tyr Asn Asn Pro  
545 550 555 560

20 Tyr Thr His Thr Val Asp Tyr Phe Ile Leu Lys Thr Ser Ser Tyr Gly  
565 570 575

25 Trp Phe Pro Thr Gly Gln Val Ser Asn Glu His Trp Glu Tyr Val Gly  
580 585 590

30 His Asp Gln Asn Ser Ala Gln Ala Leu Leu Ala Asn Arg Ile Asn Asn  
595 600 605

Lys Gly Tyr Leu Tyr His Gly Lys Leu Leu Gly Asn Ile Asn Phe Ser  
610 615 620

35 Asn Lys Ala Thr Pro Gly Thr Thr Gly Ala Leu Val Met Asp Gly Ser  
625 630 635 640

40 Ala Asn Met Ser Gly Thr Phe Thr Gln Glu Asn Gly Arg Leu Thr Ile  
645 650 655

Gln Gly His Pro Val Ile His Ala Ser Thr Ser Gln Ser Ile Ala Asn  
660 665 670

45 Thr Val Ser Ser Leu Gly Asp Asn Ser Val Leu Thr Gln Pro Thr Ser  
675 680 685

50 Phe Thr Gln Asp Asp Trp Glu Asn Arg Thr Phe Ser Phe Gly Ser Leu  
690 695 700

55

EP 1 342 784 A1

Val Leu Lys Asp Thr Asp Phe Gly Leu Gly Arg Asn Ala Thr Leu Asn  
705 710 715 720

5 Thr Thr Ile Gln Ala Asp Asn Ser Ser Val Thr Leu Gly Asp Ser Arg  
725 730 735

10 Val Phe Ile Asp Lys Lys Asp Gly Gln Gly Thr Ala Phe Thr Leu Glu  
740 745 750

15 Glu Gly Thr Ser Val Ala Thr Lys Asp Ala Asp Lys Ser Val Phe Asn  
755 760 765

Gly Thr Val Asn Leu Asp Asn Gln Ser Val Leu Asn Ile Asn Glu Ile  
770 775 780

20 Phe Asn Gly Gly Ile Gln Ala Asn Asn Ser Thr Val Asn Ile Ser Ser  
785 790 795 800

25 Asp Ser Ala Val Leu Glu Asn Ser Thr Leu Thr Ser Thr Ala Leu Asn  
805 810 815

Leu Asn Lys Gly Ala Asn Val Leu Ala Ser Gln Ser Phe Val Ser Asp  
820 825 830

30 Gly Pro Val Asn Ile Ser Asp Ala Thr Leu Ser Leu Asn Ser Arg Pro  
835 840 845

35 Asp Glu Val Ser His Thr Leu Leu Pro Val Tyr Asp Tyr Ala Gly Ser  
850 855 860

40 Trp Asn Leu Lys Gly Asp Asp Ala Arg Leu Asn Val Gly Pro Tyr Ser  
865 870 875 880

Met Leu Ser Gly Asn Ile Asn Val Gln Asp Lys Gly Thr Val Thr Leu  
885 890 895

45 Gly Gly Glu Gly Glu Leu Ser Pro Asp Leu Thr Leu Gln Asn Gln Met  
900 905 910

50 Leu Tyr Ser Leu Phe Asn Gly Tyr Arg Asn Thr Trp Ser Gly Ser Leu  
915 920 925

55 Asn Ala Pro Asp Ala Thr Val Ser Met Thr Asp Thr Gln Trp Ser Met

# EP 1 342 784 A1

	930	935	940
5	Asn Gly Asn Ser Thr Ala Gly Asn Met Lys Leu Asn Arg Thr Ile Val 945 950 955 960		
10	Gly Phe Asn Gly Gly Thr Ser Ser Phe Thr Thr Leu Thr Thr Asp Asn 965 970 975		
15	Leu Asp Ala Val Gln Ser Ala Phe Val Met Arg Thr Asp Leu Asn Lys 980 985 990		
20	Ala Asp Lys Leu Val Ile Asn Lys Ser Ala Thr Gly His Asp Asn Ser 995 1000 1005		
25	Ile Trp Val Asn Phe Leu Lys Lys Pro Ser Asp Lys Asp Thr Leu 1010 1015 1020		
30	Asp Ile Pro Leu Val Ser Ala Pro Glu Ala Thr Ala Asp Asn Leu 1025 1030 1035		
35	Phe Arg Ala Ser Thr Arg Val Val Gly Phe Ser Asp Val Thr Pro 1040 1045 1050		
40	Thr Leu Ser Val Arg Lys Glu Asp Gly Lys Lys Glu Trp Val Leu 1055 1060 1065		
45	Asp Gly Tyr Gln Val Ala Arg Asn Asp Gly Gln Gly Lys Ala Ala 1070 1075 1080		
50	Ala Thr Phe Met His Ile Ser Tyr Asn Asn Phe Ile Thr Glu Val 1085 1090 1095		
55	Asn Asn Leu Asn Lys Arg Met Gly Asp Leu Arg Asp Ile Asn Gly 1100 1105 1110		
	Glu Ala Gly Thr Trp Val Arg Leu Leu Asn Gly Ser Gly Ser Ala 1115 1120 1125		
	Asp Gly Gly Phe Thr Asp His Tyr Thr Leu Leu Gln Met Gly Ala 1130 1135 1140		
	Asp Arg Lys His Glu Leu Gly Ser Met Asp Leu Phe Thr Gly Val 1145 1150 1155		

5 Met Ala Thr Tyr Thr Asp Thr Asp Ala Ser Ala Gly Leu Tyr Ser  
1160 1165 1170

10 Gly Lys Thr Lys Ser Trp Gly Gly Gly Phe Tyr Ala Ser Gly Leu  
1175 1180 1185

15 Phe Arg Ser Gly Ala Tyr Phe Asp Leu Ile Ala Lys Tyr Ile His  
1190 1195 1200

20 Asn Glu Asn Lys Tyr Asp Leu Asn Phe Ala Gly Ala Gly Lys Gln  
1205 1210 1215

25 Asn Phe Arg Ser His Ser Leu Tyr Ala Gly Ala Glu Val Gly Tyr  
1220 1225 1230

30 Arg Tyr His Leu Thr Asp Thr Thr Phe Val Glu Pro Gln Ala Glu  
1235 1240 1245

35 Leu Val Trp Gly Arg Leu Gln Gly Gln Thr Phe Asn Trp Asn Asp  
1250 1255 1260

40 Ser Gly Met Asp Val Ser Met Arg Arg Asn Ser Val Asn Pro Leu  
1265 1270 1275

45 Val Gly Arg Thr Gly Val Val Ser Gly Lys Thr Phe Ser Gly Lys  
1280 1285 1290

50 Asp Trp Ser Leu Thr Ala Arg Ala Gly Leu His Tyr Glu Phe Asp  
1295 1300 1305

55 Leu Thr Asp Ser Ala Asp Val His Leu Lys Asp Ala Ala Gly Glu  
1310 1315 1320

His Gln Ile Asn Gly Arg Lys Asp Gly Arg Met Leu Tyr Gly Val  
1325 1330 1335

Gly Leu Asn Ala Arg Phe Gly Asp Asn Thr Arg Leu Gly Leu Glu  
1340 1345 1350

Val Glu Arg Ser Ala Phe Gly Lys Tyr Asn Thr Asp Asp Ala Ile  
1355 1360 1365

EP 1 342 784 A1

Asn Ala Asn Ile Arg Tyr Ser Phe  
1370 1375

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<210> 27  
<211> 349  
<212> PRT  
<213> Escherichia coli  
10 <400> 27

Met Ile Thr Leu Phe Arg Leu Leu Ala Ile Leu Cys Leu Phe Phe Asn  
1 5 10 15

15 Val Ser Ala Phe Ala Val Asp Cys Tyr Gln Asp Gly Tyr Arg Gly Thr  
20 25 30

Thr Leu Ile Asn Gly Asp Leu Pro Thr Phe Lys Ile Pro Glu Asn Ala  
20 35 40 45

Gln Pro Gly Gln Lys Ile Trp Glu Ser Gly Asp Ile Asn Ile Thr Val  
50 55 60

25 Tyr Cys Asp Asn Ala Pro Gly Trp Ser Ser Asn Asn Pro Ser Glu Asn  
65 70 75 80

30 Val Tyr Ala Trp Ile Lys Leu Pro Gln Ile Asn Ser Ala Asp Met Leu  
85 90 95

Asn Asn Pro Tyr Leu Thr Phe Gly Val Thr Tyr Asn Gly Val Asp Tyr  
35 100 105 110

Glu Gly Thr Asn Glu Lys Ile Asp Thr His Ala Cys Leu Asp Lys Tyr  
115 120 125

40 Glu Gln Tyr Tyr Asn Gly Tyr Tyr His Asp Pro Val Cys Asn Gly Ser  
130 135 140

45 Thr Leu Gln Lys Asn Val Thr Phe Asn Ala His Phe Arg Val Tyr Val  
145 150 155 160

Lys Phe Lys Ser Arg Pro Ala Gly Asp Gln Thr Val Asn Phe Gly Thr  
50 165 170 175

Val Asn Val Leu Gln Phe Asp Gly Glu Gly Gly Ala Asn Met Ala Pro  
180 185 190

55



5 Asn Ala Lys Asn Leu Arg Tyr Ala Ile Thr Gly Leu Asp Asn Ile Ser  
 195 200 205

10 Phe Leu Asp Cys Ser Val Asp Val Arg Ile Ser Pro Glu Ser Gln Ile  
 210 215 220

15 Val Asn Phe Gly Gln Ile Ala Ala Asn Ser Ile Ala Thr Phe Pro Pro  
 225 230 235 240

20 Lys Ala Ala Phe Ser Val Ser Thr Ile Lys Asp Ile Ala Ser Asp Cys  
 245 250 255

25 Thr Glu Gln Phe Asp Val Ala Thr Ser Phe Phe Thr Ser Asp Thr Leu  
 260 265 270

30 Tyr Asp Asn Thr His Leu Glu Ile Gly Asn Gly Leu Leu Met Arg Ile  
 275 280 285

35 Thr Asp Gln Lys Thr Gln Glu Asp Ile Lys Phe Asn Gln Phe Lys Leu  
 290 295 300

40 Phe Ser Thr Tyr Ile Pro Gly Gln Ser Ala Ala Met Ala Thr Arg Asp  
 305 310 315 320

45 Tyr Gln Ala Glu Leu Thr Gln Lys Pro Gly Glu Pro Leu Val Tyr Gly  
 325 330 335

50 Pro Phe Gln Lys Asp Leu Ile Val Lys Ile Asn Tyr His  
 340 345

55 <210> 28  
 <211> 840  
 <212> PRT  
 <213> Escherichia coli  
 <400> 28

Met Asn Asn Lys Asn Thr Phe Ser Arg Asp Lys Leu Ser His Ala Ile  
 1 5 10 15

50 Lys Asn Ala Leu Ser Gly Val Val Cys Ser Leu Leu Phe Val Leu Pro  
 20 25 30

55 Val His Ala Val Glu Phe Asn Val Asp Met Ile Asp Ala Glu Asp Arg

EP 1 342 784 A1

	35	40	45
5	Glu Asn Ile Asp Ile Ser Arg Phe Glu Lys Lys Gly Tyr Ile Pro Pro		
	50	55	60
10	Gly Arg Tyr Leu Val Arg Val Gln Ile Asn Lys Asn Met Leu Pro Gln		
	65	70	75
	Thr Leu Ile Leu Glu Trp Val Lys Ala Asp Asn Glu Ser Gly Ser Leu		
	85	90	95
15	Leu Cys Leu Thr Lys Glu Asn Leu Thr Asn Phe Gly Leu Asn Thr Glu		
	100	105	110
20	Phe Ile Glu Ser Leu Gln Asn Ile Ala Gly Ser Glu Cys Leu Asp Leu		
	115	120	125
25	Ser Gln Arg Gln Glu Leu Thr Thr Arg Leu Asp Lys Ala Thr Met Ile		
	130	135	140
	Leu Ser Leu Ser Val Pro Gln Ala Trp Leu Lys Tyr Gln Ala Thr Asn		
	145	150	155
30	Trp Thr Pro Pro Glu Phe Trp Asp Thr Gly Ile Thr Gly Phe Ile Leu		
	165	170	175
35	Asp Tyr Asn Val Tyr Ala Ser Gln Tyr Ala Pro His His Gly Asp Ser		
	180	185	190
40	Thr Gln Asn Val Ser Ser Tyr Gly Thr Leu Gly Phe Asn Leu Gly Ala		
	195	200	205
	Trp Arg Leu Arg Ser Asp Tyr Gln Tyr Asn Gln Asn Phe Ala Asp Gly		
	210	215	220
45	Arg Ser Val Asn Arg Asp Ser Glu Phe Ala Arg Thr Tyr Leu Phe Arg		
	225	230	235
50	Pro Ile Pro Ser Trp Ser Ser Lys Phe Thr Met Gly Gln Tyr Asp Leu		
	245	250	255
55	Ser Ser Asn Leu Tyr Asp Thr Phe His Phe Thr Gly Ala Ser Leu Glu		
	260	265	270

EP 1 342 784 A1

5 Ser Asp Glu Ser Met Leu Pro Pro Asp Leu Gln Gly Tyr Ala Pro Gln  
275 280 285

10 Ile Thr Gly Ile Ala Gln Thr Asn Ala Lys Val Thr Val Ala Gln Asn  
290 295 300

Gly Arg Val Leu Tyr Gln Thr Thr Val Ala Pro Gly Pro Phe Thr Ile  
305 310 315 320

15 Ser Asp Leu Gly Gln Ser Phe Gln Gly Gln Leu Asp Val Thr Val Glu  
325 330 335

20 Glu Glu Asp Gly Arg Thr Ser Thr Phe Gln Val Gly Ser Ala Ser Ile  
340 345 350

Pro Tyr Leu Thr Arg Lys Gly Gln Val Arg Tyr Lys Thr Ser Leu Gly  
355 360 365

25 Lys Pro Thr Ser Val Gly His Asn Asp Ile Asn Asn Pro Phe Phe Trp  
370 375 380

30 Thr Ala Glu Ala Ser Trp Gly Trp Leu Asn Asn Val Ser Leu Tyr Gly  
385 390 395 400

35 Gly Gly Met Phe Thr Ala Asp Asp Tyr Gln Ala Ile Thr Thr Gly Ile  
405 410 415

Gly Phe Asn Leu Asn Gln Phe Gly Ser Leu Ser Phe Asp Val Thr Gly  
420 425 430

40 Ala Asp Ala Ser Leu Gln Gln Gln Asn Ser Gly Asn Leu Arg Gly Tyr  
435 440 445

45 Ser Tyr Arg Phe Asn Tyr Ala Lys His Phe Glu Ser Thr Gly Ser Gln  
450 455 460

Ile Thr Phe Ala Gly Tyr Arg Phe Ser Asp Lys Asp Tyr Val Ser Met  
465 470 475 480

50 Ser Glu Tyr Leu Ser Ser Arg Asn Gly Asp Glu Ser Ile Asp Asn Glu  
485 490 495

55

EP 1 342 784 A1

5 Lys Glu Ser Tyr Val Ile Ser Leu Asn Gln Tyr Phe Glu Thr Leu Glu  
 500 505 510  
 10 Leu Asn Ser Tyr Leu Asn Val Thr Arg Asn Thr Tyr Trp Asp Ser Ala  
 515 520 525  
 15 Asp Phe Lys Gly Ile Ser Ala Ser Leu Ala Val Ser Arg Ile Arg Trp  
 545 550 555 560  
 20 Asp Asp Asp Glu Glu Asn Gln Tyr Tyr Phe Ser Phe Ser Leu Pro Leu  
 565 570 575  
 25 Gln Gln Asn Arg Asn Ile Ser Tyr Ser Met Gln Arg Thr Gly Ser Ser  
 580 585 590  
 30 Asn Thr Ser Gln Met Ile Ser Trp Tyr Asp Ser Ser Asp Arg Asn Asn  
 595 600 605  
 35 Ile Trp Asn Ile Ser Ala Ser Ala Thr Asp Asp Asn Ile Arg Asp Gly  
 610 615 620  
 40 Glu Pro Thr Leu Arg Gly Ser Tyr Gln His Tyr Ser Pro Trp Gly Arg  
 625 630 635 640  
 45 Leu Asn Ile Asn Gly Ser Val Gln Pro Asn Gln Tyr Asn Ser Val Thr  
 645 650 655  
 50 Ala Gly Trp Tyr Gly Ser Leu Thr Ala Thr Arg His Gly Val Ala Leu  
 660 665 670  
 55 His Asp Tyr Ser Tyr Gly Asp Asn Ala Arg Met Met Val Asp Thr Asp  
 675 680 685  
 60 Gly Ile Ser Gly Ile Glu Ile Asn Ser Asn Arg Thr Val Thr Asn Gly  
 690 695 700  
 65 Leu Gly Ile Ala Val Ile Pro Ser Leu Ser Asn Tyr Thr Thr Ser Met  
 705 710 715 720

EP 1 342 784 A1

Leu Arg Val Asn Asn Asn Asp Leu Pro Glu Gly Val Asp Val Glu Asn  
725 730 735

5 Ser Val Ile Arg Thr Thr Leu Thr Gln Gly Ala Ile Gly Tyr Ala Lys  
740 745 750

10 Leu Asn Ala Thr Thr Gly Tyr Gln Ile Val Gly Val Ile Arg Gln Glu  
755 760 765

15 Asn Gly Arg Phe Pro Pro Leu Gly Val Asn Val Thr Asp Lys Ala Thr  
770 775 780

Gly Lys Asp Val Gly Leu Val Ala Glu Asp Gly Phe Val Tyr Leu Ser  
785 790 795 800

20 Gly Ile Gln Glu Asn Ser Ile Leu His Leu Thr Trp Gly Asp Asn Thr  
805 810 815

25 Cys Glu Val Thr Pro Pro Asn Gln Ser Asn Ile Ser Glu Ser Ala Ile  
820 825 830

Ile Leu Pro Cys Lys Thr Val Lys  
835 840

30

<210> 29  
<211> 169  
<212> PRT  
<213> Escherichia coli  
<400> 29

35

Leu Met Asn Thr Lys Gln Ser Val Ala Gln Leu Ala Val Pro His Arg  
1 5 10 15

40

Lys Arg Leu Ser Ser Thr Met Val Val Ala Leu Leu Leu Cys Val Val  
20 25 30

45

Ala Gly Ala Val Met Ile Asn Ala Ala Asp Phe Pro Ala Thr Ala Ile  
35 40 45

Glu Thr Asp Pro Gly Ala Ser Ala Phe Pro Thr Phe Tyr Ala Cys Ala  
50 55 60

55

Leu Ile Val Leu Ala Val Leu Leu Val Ile Arg Asp Leu Leu Gln Ala  
65 70 75 80

EP 1 342 784 A1

5 Lys Pro Ala Ser Cys Ala Asn Ala Gln Glu Lys Pro Ala Phe Arg Lys  
 85 90 95  
 Thr Ala Thr Gly Ile Ala Ala Thr Ala Phe Tyr Ile Val Ala Met Ser  
 100 105 110  
 10 Tyr Cys Gly Tyr Leu Ile Thr Thr Pro Val Phe Leu Ile Val Ile Met  
 115 120 125  
 15 Thr Leu Met Gly Tyr Arg Arg Trp Val Leu Thr Pro Gly Ile Ala Leu  
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 Leu Leu Thr Ala Ile Leu Trp Leu Leu Phe Val Glu Ala Leu Gln Val  
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 20 Pro Leu Pro Val Gly Thr Phe Phe Glu  
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 30 Met Val Leu Leu Ala Gly Ala Ala Leu Ser Ile Ala Pro Val Gln Ala  
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 35 Ala Ser Tyr Pro Thr Lys Gln Ile Glu Leu Val Val Pro Tyr Ala Ala  
 20 25 30  
 Gly Gly Gly Thr Asp Leu Val Ala Arg Ala Phe Ala Asp Ala Ala Lys  
 35 40 45  
 40 Asn His Leu Pro Val Ser Ile Gly Val Ile Asn Lys Pro Gly Gly Gly  
 50 55 60  
 45 Gly Ala Ile Gly Leu Ser Glu Ile Ala Ala Ala Arg Pro Asn Gly Tyr  
 65 70 75 80  
 50 Lys Ile Gly Leu Gly Thr Val Glu Leu Thr Thr Leu Pro Ser Leu Gly  
 85 90 95  
 55 Met Val Arg Phe Lys Thr Ser Asp Phe Lys Pro Ile Ala Arg Leu Asn  
 100 105 110

EP 1.342 784 A1

5 Ala Asp Pro Ala Ala Ile Thr Val Arg Ala Asp Ala Pro Trp Asn Ser  
115 120 125

Tyr Glu Glu Phe Met Ala Tyr Ser Lys Ala Asn Pro Gly Lys Val Arg  
130 135 140

10 Ile Gly Asn Ser Gly Thr Gly Ala Ile Trp His Leu Ala Ala Ala Ala  
145 150 155 160

15 Leu Glu Asp Lys Thr Gly Thr Lys Phe Ser His Val Pro Tyr Asp Gly  
165 170 175

20 Ala Ala Pro Ala Ile Thr Gly Leu Leu Gly Gly His Ile Glu Ala Val  
180 185 190

Ser Val Ser Pro Gly Glu Val Ile Asn His Val Asn Gly Gly Lys Leu  
195 200 205

25 Lys Thr Leu Val Val Met Ala Asp Glu Arg Met Lys Thr Met Pro Asp  
210 215 220

30 Val Pro Thr Leu Lys Glu Lys Gly Val Asp Leu Ser Ile Gly Thr Trp  
225 230 235 240

35 Arg Gly Leu Ile Val Ser Gln Lys Thr Pro Gln Asp Val Val Asp Val  
245 250 255

Leu Ala Lys Ala Ala Lys Glu Thr Ala Glu Glu Pro Ala Phe Gln Asp  
260 265 270

40 Ala Leu Gln Lys Leu Asn Leu Asn Tyr Ala Trp Leu Asp Ala Ala Ser  
275 280 285

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EP 1 342 784 A1

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15 Asp Leu Gly Ser Gln Ala Ala Gln Gln Asp Glu Gln Thr Asn Lys Gly  
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Lys Ser Leu Lys Glu Arg Gly Ala Asp Tyr Val Ile Asn Ser Ala Thr  
50 55 60

20 Gln Gly Phe Glu Asn Leu Thr Pro Glu Ala Leu Glu Ser Gln Ala Arg  
65 70 75 80

25 Ser Tyr Leu Gln Ser Gln Ile Thr Ser Thr Ala Gln Ser Tyr Ile Glu  
85 90 95

30 Asp Thr Leu Ser Pro Tyr Gly Lys Val Arg Leu Asn Leu Ser Ile Gly  
100 105 110

Gln Gly Gly Asp Leu Asp Gly Ser Ser Ile Asp Tyr Phe Val Pro Trp  
115 120 125

35 Tyr Asp Asn Gln Thr Thr Val Tyr Phe Ser Gln Phe Ser Ala Gln Arg  
130 135 140

40 Lys Glu Asp Arg Thr Ile Gly Asn Ile Gly Leu Gly Val Arg Tyr Asn  
145 150 155 160

Phe Asp Lys Tyr Leu Leu Gly Gly Asn Ile Phe Tyr Asp Tyr Asp Phe  
165 170 175

45 Thr Arg Gly His Arg Arg Leu Gly Leu Gly Ala Glu Ala Trp Thr Asp  
180 185 190

50 Tyr Leu Lys Phe Ser Gly Asn Tyr Tyr His Pro Leu Ser Asp Trp Lys  
195 200 205

55 Asp Ser Glu Asp Phe Asp Phe Tyr Glu Glu Arg Pro Ala Arg Gly Trp  
210 215 220



EP 1.342 784 A1

5 Asp Ile Arg Ala Glu Val Trp Leu Pro Ser Tyr Pro Gln Leu Gly Gly  
225 230 235 240

10 Lys Ile Val Phe Glu Gln Tyr Tyr Gly Asp Glu Val Ala Leu Phe Gly  
245 250 255

15 Thr Asp Asn Leu Glu Lys Asp Pro Tyr Ala Val Thr Leu Gly Leu Asn  
260 265 270

20 Tyr Gln Pro Val Pro Leu Leu Thr Val Gly Thr Asp Tyr Lys Ala Gly  
275 280 285

25 Thr Gly Asp Asn Ser Asp Val Ser Ile Asn Ala Thr Leu Asn Tyr Gln  
290 295 300

30 Phe Gly Val Pro Leu Lys Asp Gln Leu Asp Ser Asp Lys Val Lys Ala  
305 310 315 320

35 Ala His Ser Leu Met Gly Ser Arg Leu Asp Phe Val Glu Arg Asn Asn  
325 330 335

40 Phe Ile Val Leu Glu Tyr Lys Glu Lys Asp Pro Leu Asp Val Thr Leu  
340 345 350

45 Trp Leu Lys Ala Asp Ala Thr Asn Glu His Pro Glu Cys Val Ile Lys  
355 360 365

50 Asp Thr Pro Glu Ala Ala Val Gly Leu Glu Lys Cys Lys Trp Thr Ile  
370 375 380

55 Asn Ala Leu Ile Asn His His Tyr Lys Ile Val Ala Ala Ser Trp Gln  
385 390 395 400

Ala Lys Asn Asn Ala Ala Arg Thr Leu Val Met Pro Val Ile Lys Glu  
405 410 415

Asn Thr Leu Thr Glu Gly Asn Asn Asn His Trp Asn Leu Val Leu Pro  
420 425 430

Ala Trp Gln Tyr Ser Ser Asp Gln Ala Glu Gln Glu Lys Leu Asn Thr  
435 440 445

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EP 1 342 784 A1

5 Trp Arg Val Arg Leu Ala Leu Glu Asp Glu Lys Gly Asn Arg Gln Asn  
450 455 460

10 Ser Gly Val Val Glu Ile Thr Val Gln Gln Asp Arg Lys Ile Glu Leu  
465 470 475 480

15 Ile Val Asn Asn Ile Ala Asn Pro Glu Glu Asn Asn His Ser His Glu  
485 490 495

20 Ala Ser Ala Gln Ala Asp Gly Val Asp Gly Val Val Met Asp Leu Asp  
500 505 510

25 Val Thr Asp Ser Phe Gly Asp Asn Thr Asp Arg Asn Gly Asp Ala Leu  
515 520 525

30 Pro Glu Asp Asn Leu Thr Pro Gln Leu Tyr Asp Ala Gln Asp Lys Arg  
530 535 540

35 Val Thr Leu Thr Asn Lys Pro Cys Ser Thr Asp Asn Pro Cys Val Phe  
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40 Ile Ala Lys Gln Asp Lys Glu Lys Gly Thr Val Thr Leu Ser Ser Thr  
565 570 575

45 Leu Pro Gly Thr Tyr Arg Trp Lys Ala Lys Ala Ala Pro Tyr Asp Asp  
580 585 590

50 Ser Asn Tyr Val Asp Val Thr Phe Leu Gly Ala Glu Ile Gly Gly Leu  
595 600 605

55 Asn Ala Phe Ile Tyr Arg Val Gly Ala Ala Lys Pro Ser Asn Leu Ile  
610 615 620

60 Gly Lys Asp Lys Glu Pro Leu Pro Ser Thr Thr Phe Ile Asp Leu Phe  
625 630 635 640

65 Tyr Gly Ala Thr Thr Ile Lys Thr Val Ser Ser Ser Arg Ser Lys Asn  
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70 Leu Thr Lys Arg Trp Cys Ser Thr Thr Thr Ser Gly Asn Leu Pro Ala  
660 665 670

EP 1 342 784 A1

Arg Ala Ser Met Val Ser Gly Cys Thr Gly Glu His Ser Asn Glu Asp  
675 680 685

5 Ile Val Ile Pro Ala Thr Asn Arg Glu Ala Ala Gln Thr Tyr Gly Ala  
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Lys Lys

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Ala Trp Val Asp Ser Gly Glu Thr Asn Ile Phe Gln Gly Thr Ile Pro  
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Trp Leu Tyr Ser Glu Gly Gly Ser Ala Thr Thr Asp Ala Asp Arg Val  
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Thr Leu Thr Ser Asp Leu Lys Gly Ala Arg Pro Gln Gly Met Lys Arg  
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Thr Ser Val Phe Thr Arg Val Ile Asn Ile Gly Asp Thr Glu Gly Asp  
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Val Asp Leu Gly Gly Leu Gly Asp Asn Ala Lys Thr Ile Asp Thr Ile  
100 105 110

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Arg Trp Met Ser Tyr Lys Asp Ala Gln Gly Gly Asp Pro Lys Glu Leu  
115 120 125

Ala Thr Lys Val Thr Ser Tyr Thr Leu Thr Asp Ala Asp Arg Gly Arg  
130 135 140

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EP 1 342 784 A1

Tyr Ile Gly Ile Glu Ile Thr Pro Thr Thr Gln Thr Gly Thr Pro Asn  
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 Val Gly Thr Ala Leu His Leu Tyr Asp Val Ser Thr Ala Ser Gly Gly  
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 Gly Ser Asp Ser Asp Asn Val Ala Pro Gly Pro Val Val Asn Gln Asn  
 180 185 190  
 15  
 Leu Lys Val Ala Ile Phe Val Asp Gly Thr Ser Ile Asn Leu Ile Asn  
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 Gly Ser Thr Pro Ile Glu Leu Gly Lys Thr Tyr Val Ala Lys Leu Tyr  
 210 215 220  
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 Ser Asp Glu Asn Lys Asn Gly Lys Phe Asp Ala Gly Thr Asp Ala Asp  
 225 230 235 240  
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 Val Thr Ala Asn Tyr Asp Phe Arg Trp Val Leu Ser Gly Ser Ser Gln  
 245 250 255  
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 Gln Leu Gly Thr Ser Gly Gly Ile Val Asn Ser Ser Phe Asp Asn Asn  
 260 265 270  
 Asn Leu Val Ile Pro Ala Thr Asn Asp Glu Ala Arg Thr Asn Leu Asn  
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 Gly Pro Ala Arg Asp Gly Lys Glu Ala Leu Ser Ile Pro Thr Asn Gly  
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EP 1 342 784 A1

5 Ser Phe Asp Asp Thr Asn Ser Thr Ile Val Leu Lys Asp Arg Arg Thr  
35 40 45

10 Asn His Pro Ile Thr Pro Gln Glu Leu Phe Phe Leu Thr Leu Pro Asp  
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15 Glu Thr Lys Ile His Thr Ala Asp Phe Lys Ile Lys His Ile Lys Lys  
65 70 75 80

20 Gln Asp Asn Ala Ile Val Ile Asp Phe Thr Arg Pro Asp Phe Asn Val  
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25 Thr Val Gln Leu Asn Leu Val Lys Gly Lys Tyr Ala Ser Ile Asp Tyr  
100 105 110

30 Thr Ile Ala Ala Val Gly Gln Pro Arg Asp Val Ala Lys Ile Thr Phe  
115 120 125

35 Phe Pro Thr Lys Lys Gln Phe Gln Ala Pro Tyr Val Asp Gly Ala Ile  
130 135 140

40 Thr Ser Ser Pro Ile Ile Ala Asp Ser Phe Phe Ile Leu Pro Asn Lys  
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45 Pro Ile Val Asn Thr Tyr Ala Tyr Glu Ala Thr Thr Asn Leu Asn Val  
165 170 175

50 Glu Leu Lys Thr Pro Ile Gln Pro Glu Thr Pro Val Ser Phe Thr Thr  
180 185 190

55 Trp Phe Gly Thr Phe Pro Glu Thr Ser Gln Leu Arg Arg Ser Val Asn  
195 200 205

Gln Phe Ile Asn Ala Val Arg Pro Arg Pro Tyr Lys Pro Tyr Leu His  
210 215 220

Tyr Asn Ser Trp Met Asp Ile Gly Phe Phe Thr Pro Tyr Thr Glu Gln  
225 230 235 240

Asp Val Leu Gly Arg Met Asp Glu Trp Asn Lys Glu Phe Ile Ser Gly  
245 250 255

EP 1 342 784 A1

Arg Gly Val Ala Leu Asp Ala Phe Leu Leu Asp Asp Gly Trp Asp Asp  
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 Leu Thr Gly Arg Trp Leu Phe Gly Pro Ala Phe Ser Asn Gly Phe Ser  
 275 280 285  
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 Lys Val Arg Glu Lys Ala Asp Ser Leu His Ser Ser Val Gly Leu Trp  
 290 295 300  
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 Leu Ser Pro Trp Gly Gly Tyr Asn Lys Pro Gln Arg Arg Ser Arg Phe  
 305 310 315 320  
 Ala Cys Lys Arg Val Trp Val Arg Asn Arg Gly Arg Gln Ala Gly Ala  
 325 330 335  
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 Phe Gly Ser Glu Leu Leu Lys Asn Phe Asn Glu Gln Ile Ile Asn Leu  
 340 345 350  
 25  
 Ile Lys Asn Glu His Ile Thr Ser Phe Lys Leu Asp Gly Met Gly Asn  
 355 360 365  
 Ala Ser Ser His Ile Lys Gly Ser Pro Phe Ala Ser Asp Phe Asp Ala  
 370 375 380  
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 Ser Ile Ala Leu Leu His Asn Met Arg Arg Ala Asn Pro Asn Leu Phe  
 385 390 395 400  
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 Ile Asn Leu Thr Thr Gly Thr Asn Ala Ser Pro Ser Trp Leu Phe Tyr  
 405 410 415  
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 Ala Asp Ser Ile Trp Arg Gln Gly Asp Asp Ile Asn Leu Tyr Gly Pro  
 420 425 430  
 Gly Thr Pro Val Gln Gln Trp Ile Thr Tyr Arg Asp Ala Glu Thr Tyr  
 435 440 445  
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 Arg Ser Ile Val Arg Lys Gly Pro Leu Phe Pro Leu Asn Ser Leu Met  
 450 455 460  
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 Tyr His Gly Ile Val Ser Ala Glu Asn Ala Tyr Tyr Gly Leu Glu Lys  
 465 470 475 480  
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EP 1 342 784 A1

Val Gln Thr Asp Ser Asp Phe Ala Asp Gln Val Trp Ser Tyr Phe Ala  
485 490 495

5 Thr Gly Thr Gln Leu Gln Glu Leu Tyr Ile Thr Pro Ser Met Leu Asn  
500 505 510

10 Lys Val Lys Trp Asp Thr Leu Ala Lys Ala Ala Lys Trp Ser Lys Glu  
515 520 525

15 Asn Ala Ser Val Leu Val Asp Thr His Trp Ile Gly Gly Asp Pro Thr  
530 535 540

Ala Leu Ala Val Tyr Gly Trp Ala Ser Trp Ser Lys Asp Lys Ala Ile  
545 550 555 560

20 Leu Gly Leu Arg Asn Pro Ser Asp Lys Pro Gln Thr Tyr Tyr Leu Asp  
565 570 575

25 Leu Ala Lys Asp Phe Glu Ile Pro Ala Gly Asn Ala Ala Gln Phe Ser  
580 585 590

30 Leu Lys Ala Val Tyr Gly Ser Asn Lys Thr Val Pro Val Glu Tyr Lys  
595 600 605

Asn Ala Thr Val Ile Thr Leu Gln Pro Leu Glu Thr Leu Val Phe Glu  
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35 Ala Val Thr Ile Asn  
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50 Ser Lys Leu Leu Ile Ser Ala Leu Val Ala Gly Gly Leu Leu Ser Ser  
35 40 45

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# EP 1 342 784 A1

Phe Gly Ala Ser Ala Asp Asn Tyr Thr Gly Gln Pro Thr Asp Tyr Gly  
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Asp Gly Ser Ala Gly Asp Gly Trp Val Ala Ile Gly Lys Gly Ala Lys  
 65 70 75 80

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Ala Asn Thr Phe Met Asn Thr Ser Gly Ala Ser Thr Ala Leu Gly Tyr  
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Asp Ala Ile Ala Glu Gly Glu Tyr Ser Ser Ala Ile Gly Ser Lys Thr  
 100 105 110

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Leu Ala Thr Gly Gly Ala Ser Met Ala Phe Gly Val Ser Ala Lys Ala  
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Met Gly Asp Arg Ser Val Ala Leu Gly Ala Ser Ser Val Ala Asn Gly  
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Asp Arg Ser Met Ala Phe Gly Arg Tyr Ala Lys Thr Asn Gly Phe Thr  
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Ser Leu Ala Ile Gly Asp Ser Ser Leu Ala Asp Gly Glu Lys Thr Ile  
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Ala Leu Gly Asn Thr Ala Lys Ala Tyr Glu Ile Met Ser Ile Ala Leu  
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Gly Asp Asn Ala Asn Ala Ser Lys Glu Tyr Ala Met Ala Leu Gly Ala  
 195 200 205

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Ser Ser Lys Ala Gly Gly Ala Asp Ser Leu Ala Phe Gly Arg Lys Ser  
 210 215 220

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Thr Ala Asn Ser Thr Gly Ser Leu Ala Ile Gly Ala Asp Ser Ser Ser  
 225 230 235 240

Ser Asn Asp Asn Ala Ile Ala Ile Gly Asn Lys Thr Gln Ala Leu Gly  
 245 250 255

Val Asn Ser Met Ala Leu Gly Asn Ala Ser Gln Ala Ser Gly Glu Ser  
 260 265 270



EP 1 342 784 A1

Ser Ile Ala Leu Gly Asn Thr Ser Glu Ala Ser Glu Gln Asn Ala Ile  
 275 280 285  
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 Ala Leu Gly Gln Gly Ser Ile Ala Ser Lys Val Asn Ser Ile Ala Leu  
 290 295 300  
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 Gly Ser Asn Ser Leu Ser Ser Gly Glu Asn Ala Ile Ala Leu Gly Glu  
 305 310 315 320  
 Gly Ser Ala Ala Gly Gly Ser Asn Ser Leu Ala Phe Gly Ser Gln Ser  
 325 330 335  
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 Arg Ala Asn Gly Asn Asp Ser Val Ala Ile Gly Val Gly Ala Ala Ala  
 340 345 350  
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 Ala Thr Asp Asn Ser Val Ala Ile Gly Ala Gly Ser Thr Thr Asp Ala  
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 Ser Asn Thr Val Ser Val Gly Asn Ser Ala Thr Lys Arg Lys Ile Val  
 370 375 380  
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 Asn Met Ala Ala Gly Ala Ile Ser Asn Thr Ser Thr Asp Ala Ile Asn  
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 Gly Ser Gln Leu Tyr Thr Ile Ser Asp Ser Val Ala Lys Arg Leu Gly  
 405 410 415  
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 Gly Gly Ala Thr Val Gly Ser Asp Gly Thr Val Thr Ala Val Ser Tyr  
 420 425 430  
 Ala Leu Arg Ser Gly Thr Tyr Asn Asn Val Gly Asp Ala Leu Ser Gly  
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 Ile Asp Asn Asn Thr Leu Gln Trp Asn Lys Thr Ala Gly Ala Phe Ser  
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 Ala Asn His Gly Ala Asn Ala Thr Asn Lys Ile Thr Asn Val Ala Lys  
 465 470 475 480  
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 Gly Thr Val Ser Ala Thr Ser Thr Asp Val Val Asn Gly Ser Gln Leu  
 485 490 495  
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 Tyr Asp Leu Gln Gln Asp Ala Leu Leu Trp Asn Gly Thr Ala Phe Ser

EP 1 342 784 A1

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5	Ala Ala His Gly Thr Glu Ala Thr Ser Lys Ile Thr Asn Val Thr Ala 515 520 525		
10	Gly Asn Leu Thr Ala Gly Ser Thr Asp Ala Val Asn Gly Ser Gln Leu 530 535 540		
15	Lys Thr Thr Asn Asp Asn Val Thr Thr Asn Thr Thr Asn Ile Ala Thr 545 550 555 560		
20	Asn Thr Thr Asn Ile Thr Asn Leu Thr Asp Ala Val Asn Gly Leu Gly 565 570 575		
25	Asp Asp Ser Leu Leu Trp Asn Lys Ala Ala Gly Ala Phe Ser Ala Ala 580 585 590		
30	His Gly Thr Glu Ala Thr Ser Lys Ile Thr Asn Val Thr Ala Gly Asn 595 600 605		
35	Leu Thr Ala Gly Ser Thr Asp Ala Val Asn Gly Ser Gln Leu Lys Thr 610 615 620		
40	Thr Asn Asp Asn Val Thr Thr Asn Thr Thr Asn Ile Ala Thr Asn Thr 625 630 635 640		
45	Thr Asn Ile Thr Asn Leu Thr Asp Ala Val Asn Gly Leu Gly Asp Asp 645 650 655		
50	Ser Leu Leu Trp Asn Lys Thr Ala Gly Ala Phe Ser Ala Ala His Gly 660 665 670		
55	Thr Asp Ala Thr Ser Lys Ile Thr Asn Val Thr Ala Gly Asn Leu Thr 675 680 685		
	Ala Gly Ser Thr Asp Ala Val Asn Gly Ser Gln Leu Lys Thr Thr Asn 690 695 700		
	Asp Asn Val Thr Thr Asn Thr Thr Asn Ile Ala Thr Asn Thr Thr Asn 705 710 715 720		
	Ile Thr Asn Leu Thr Asp Ala Val Asn Gly Leu Gly Asp Asp Ser Leu 725 730 735		

EP 1 342 784 A1

5 Leu Trp Asn Lys Thr Ala Gly Ala Phe Ser Ala Ala His Gly Thr Asp  
740 745 750

Ala Thr Ser Lys Ile Thr Asn Val Lys Ala Gly Asp Leu Thr Ala Gly  
755 760 765

10 Ser Thr Asp Ala Val Asn Gly Ser Gln Leu Lys Thr Thr Asn Asp Asn  
770 775 780

15 Val Ser Thr Asn Thr Thr Asn Ile Thr Asn Leu Thr Asp Ala Val Asn  
785 790 795 800

20 Gly Leu Gly Asp Asp Ser Leu Leu Trp Asn Lys Thr Ala Gly Ala Phe  
805 810 815

Ser Ala Ala His Gly Thr Asp Ala Thr Ser Lys Ile Thr Asn Val Lys  
820 825 830

25 Ala Gly Asp Leu Thr Ala Gly Ser Thr Asp Ala Val Asn Gly Ser Gln  
835 840 845

30 Leu Lys Thr Thr Asn Asp Asn Val Ser Thr Asn Thr Thr Asn Ile Thr  
850 855 860

35 Asn Leu Thr Asp Ser Val Gly Asp Leu Lys Asp Asp Ser Leu Leu Trp  
865 870 875 880

Asn Lys Ala Ala Gly Ala Phe Ser Ala Ala His Gly Thr Glu Ala Thr  
885 890 895

40 Ser Lys Ile Thr Asn Leu Leu Ala Gly Lys Ile Ser Ser Asn Ser Thr  
900 905 910

45 Asp Ala Ile Asn Gly Ser Gln Leu Tyr Gly Val Ala Asp Ser Phe Thr  
915 920 925

50 Ser Tyr Leu Gly Gly Gly Ala Asp Ile Ser Asp Thr Gly Val Leu Ser  
930 935 940

Gly Pro Thr Tyr Thr Ile Gly Gly Thr Asp Tyr Thr Asn Val Gly Asp  
945 950 955 960

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EP 1 342 784 A1

Ala Leu Ala Ala Ile Asn Thr Ser Phe Ser Thr Ser Leu Gly Asp Ala  
965 970 975

5

Leu Leu Trp Asp Ala Thr Ala Gly Lys Phe Ser Ala Lys His Gly Ile  
980 985 990

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Asn Asn Ala Pro Ser Val Ile Thr Asp Val Ala Asn Gly Ala Val Ser  
995 1000 1005

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Ser Thr Ser Ser Asp Ala Ile Asn Gly Ser Gln Leu Tyr Gly Val  
1010 1015 1020

Ser Asp Tyr Ile Ala Asp Ala Leu Gly Gly Asn Ala Val Val Asn  
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Thr Asp Gly Ser Ile Thr Thr Pro Thr Tyr Ala Ile Ala Gly Gly  
1040 1045 1050

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Ser Tyr Asn Asn Val Gly Asp Ala Leu Glu Ala Ile Asp Thr Thr  
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Leu Asp Asp Ala Leu Leu Trp Asp Thr Thr Ala Asn Gly Gly Asn  
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Gly Ala Phe Ser Ala Ala His Gly Lys Asp Lys Thr Ala Ser Val  
1085 1090 1095

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Ile Thr Asn Val Ala Asn Gly Ala Val Ser Ala Thr Ser Asn Asp  
1100 1105 1110

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Ala Ile Asn Gly Ser Gln Leu Tyr Ser Thr Asn Lys Tyr Ile Ala  
1115 1120 1125

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Asp Ala Leu Gly Gly Asp Ala Glu Val Asn Ala Asp Gly Thr Ile  
1130 1135 1140

Thr Ala Pro Thr Tyr Thr Ile Ala Asn Thr Asp Tyr Asn Asn Val  
1145 1150 1155

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Gly Glu Ala Leu Asp Ala Leu Asp Asn Asn Ala Leu Leu Trp Asp  
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EP 1 342 784 A1

	Glu Asp	Ala Gly	Ala Tyr	Asn Ala	Ser His	Asp Gly	Asn Ala	Ser	
	1175			1180			1185		
5	Lys Ile	Thr Asn	Val Ala	Ala Ala	Gly Asp	Leu Ser	Thr Thr	Ser Thr	
	1190			1195			1200		
10	Asp Ala	Val Asn	Gly Ser	Gln Leu	Asn Ala	Thr Asn	Ile Leu	Val	
	1205			1210			1215		
15	Thr Gln	Asn Ser	Gln Met	Ile Asn	Gln Leu	Ala Gly	Asn Thr	Ser	
	1220			1225			1230		
20	Glu Thr	Tyr Ile	Glu Glu	Asn Gly	Ala Gly	Ile Asn	Tyr Val	Arg	
	1235			1240			1245		
25	Thr Asn	Asp Ser	Gly Leu	Ala Phe	Asn Asp	Ala Ser	Ala Ser	Gly	
	1250			1255			1260		
30	Ile Gly	Ala Thr	Ala Val	Gly Tyr	Asn Ala	Val Ala	Ser His	Ala	
	1265			1270			1275		
35	Ser Ser	Val Ala	Ile Gly	Gln Asp	Ser Ile	Ser Glu	Val Asp	Thr	
	1280			1285			1290		
40	Gly Ile	Ala Leu	Gly Ser	Ser Ser	Ser Val	Ser Ser	Arg Val	Ile Val	
	1295			1300			1305		
45	Lys Gly	Thr Arg	Asn Thr	Ser Val	Ser Glu	Glu Gly	Val Val	Ile	
	1310			1315			1320		
50	Gly Tyr	Asp Thr	Thr Asp	Gly Glu	Leu Leu	Gly Ala	Leu Ser	Ile	
	1325			1330			1335		
55	Gly Asp	Asp Gly	Lys Tyr	Arg Gln	Ile Ile	Asn Val	Ala Asp	Gly	
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60	Ser Glu	Ala His	Asp Ala	Val Thr	Val Arg	Gln Leu	Gln Asn	Ala	
	1355			1360			1365		
65	Ile Gly	Ala Val	Ala Thr	Thr Pro	Thr Lys	Tyr Tyr	His Ala	Asn	
	1370			1375			1380		
70	Ser Thr	Ala Glu	Asp Ser	Leu Ala	Val Gly	Glu Asp	Ser Leu	Ala	

# EP 1 342 784 A1

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10	Gly Leu Asn Thr Leu Val Leu	Ala Asp Ala Ile Asn	Gly Ile Ala		
	1415	1420	1425		
15	Ile Gly Ser Asn Ala Arg Ala	Asn His Ala Asp Ser	Ile Ala Met		
	1430	1435	1440		
20	Gly Asn Gly Ser Gln Thr Thr	Arg Gly Ala Gln Thr	Asn Tyr Thr		
	1445	1450	1455		
25	Ala Tyr Asn Met Asp Ala Pro	Gln Asn Ser Val Gly	Glu Phe Ser		
	1460	1465	1470		
30	Val Gly Ser Glu Asp Gly Gln	Arg Gln Ile Thr Asn	Val Ala Ala		
	1475	1480	1485		
35	Gly Ser Ala Asp Thr Asp Ala	Val Asn Val Gly Gln	Leu Lys Val		
	1490	1495	1500		
40	Thr Asp Ala Gln Val Ser Gln	Asn Thr Gln Ser Ile	Thr Asn Leu		
	1505	1510	1515		
45	Asn Thr Gln Val Thr Asn Leu	Asp Thr Arg Val Thr	Asn Ile Glu		
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50	Asn Gly Ile Gly Asp Ile Val	Thr Thr Gly Ser Thr	Lys Tyr Phe		
	1535	1540	1545		
55	Lys Thr Asn Thr Asp Gly Ala	Asp Ala Asn Ala Gln	Gly Lys Asp		
	1550	1555	1560		
60	Ser Val Ala Ile Gly Ser Gly	Ser Ile Ala Ala Ala	Asp Asn Ser		
	1565	1570	1575		
65	Val Ala Leu Gly Thr Gly Ser	Val Ala Asp Glu Glu	Asn Thr Ile		
	1580	1585	1590		
70	Ser Val Gly Ser Ser Thr Asn	Gln Arg Arg Ile Thr	Asn Val Ala		
	1595	1600	1605		

EP 1 342 784 A1

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20 Thr Thr Arg Ile Ser Asn Val Ser Ala Gly Val Asn Asn Asn Asp  
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25 Ala Val Asn Tyr Ala Gln Leu Lys Gln Ser Val Gln Glu Thr Lys  
1670 1675 1680

30 Gln Tyr Thr Asp Gln Arg Met Val Glu Met Asp Asn Lys Leu Ser  
1685 1690 1695

35 Lys Thr Glu Ser Lys Leu Ser Gly Gly Ile Ala Ser Ala Met Ala  
1700 1705 1710

40 Met Thr Gly Leu Pro Gln Ala Tyr Thr Pro Gly Ala Ser Met Ala  
1715 1720 1725

45 Ser Ile Gly Gly Gly Thr Tyr Asn Gly Glu Ser Ala Val Ala Leu  
1730 1735 1740

50 Gly Val Ser Met Val Ser Ala Asn Gly Arg Trp Val Tyr Lys Leu  
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55 Gln Gly Ser Thr Asn Ser Gln Gly Glu Tyr Ser Ala Ala Leu Gly  
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Ala Gly Ile Gln Trp  
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EP 1 342 784 A1

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5	Cys	Leu	Leu	Val
		20		
	Gly	Cys	Asp	Tyr
			25	
	Ile	Glu	Lys	Ala
				30
	Ser	Lys	Val	Asp
10	Asp	Leu	Val	Thr
		35		
	Gln	Gln	Glu	Leu
			40	
	Lys	Ser	Lys	Ile
				45
	Glu	Lys	Gln	Gln
		50		
	Glu	Leu	Asp	Lys
			55	
	Arg	Lys	Ile	Glu
				60
	His	Phe	Glu	Lys
15	Gln	Gln	Thr	Thr
			70	
	Ile	Ile	Asn	Ser
				75
	Thr	Lys	Thr	Leu
				80
	Ala	Gly	Val	Val
20	Lys	Ala	Val	Lys
				85
	Asn	Lys	Gln	Asp
				90
	Glu	Phe	Val	Phe
				95
	Thr	Glu	Phe	Asn
25	Pro	Ala	Gln	Thr
			100	
	Gln	Tyr	Phe	Ile
				105
	Leu	Asn	Asn	Gly
				110
	Ser	Val	Gly	Leu
30	Ala	Gly	Lys	Ile
			115	
	Leu	Ser	Ile	Asp
				120
	Ala	Val	Glu	Asn
				125
	Gly	Ser	Val	Ile
35	Arg	Ile	Ser	Leu
				130
	Val	Asn	Leu	Leu
				135
	Ser	Val	Pro	Val
				140
	Ser	Asn	Met	Gly
40	Phe	Tyr	Ala	Thr
				145
	Trp	Gly	Gly	Glu
				150
	Lys	Pro	Thr	Asp
				155
	Ile	Asn	Ala	Leu
				160
	Ala	Lys	Trp	Gln
				165
	Gln	Leu	Leu	Phe
				170
	Ser	Thr	Ala	Met
				175
	Asn	Ser	Ser	Leu
45	Lys	Leu	Leu	Pro
				180
	Gly	Gln	Trp	Gln
				185
	Asp	Ile	Asn	Leu
				190
	Thr	Leu	Lys	Gly
50	Val	Ser	Pro	Asn
				195
	Asn	Asn	Leu	Lys
				200
	Tyr	Leu	Lys	Leu
				205
	Ala	Ile	Asn	Met
				210
	Ala	Glu	Ser	Pro
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	Gln	Arg	Lys	
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55	Asn	Lys	Lys	
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 20 25 30

Ser Ala Gln Asp Glu His Ala Val Trp Leu Arg Leu Leu Ile Thr Ala  
 35 40 45

20 Ile Val Ile Cys Leu Leu Ser Met Cys Ile Phe Phe Leu Phe Ser Phe  
 50 55 60

25 Arg Gln Asn Glu Ala Ser Thr Ile Ser Leu Tyr Ala Gln Pro Thr Asp  
 65 70 75 80

Ile Lys Glu Ile Asn Thr Glu Gln Pro Asn Tyr Ala Ser Leu Leu Thr  
 85 90 95

30 Ile Tyr Leu Arg Asp Arg Tyr Gly Pro Phe Trp Arg Arg Lys Val Arg  
 100 105 110

35 Leu Leu Leu Val Thr Gly Glu Pro Glu Gln Ala Glu Ala Ile Ala Pro  
 115 120 125

40 Gly Leu Thr Gly Gln His Trp Leu Glu Gly Asp His Thr Val Leu Ile  
 130 135 140

Tyr Gly Gly Arg Pro Thr Ala Glu Pro Asp Val Thr Leu Leu Thr Ala  
 145 150 155 160

45 Leu Lys Lys Leu Arg Arg Ser Arg Pro Leu Asp Gly Ile Ile Trp Ala  
 165 170 175

50 Leu Thr Glu Glu Gln Ser Arg Gln Thr Ala Gln Leu Asp Lys Gly Trp  
 180 185 190

55 Arg Gly Leu Ile Asn Gly Gly Lys Arg Leu Gly Phe Gln Ala Pro Leu

EP 1 342 784 A1

	195	200	205
5	Tyr Leu Trp Gln Val Cys Asp Asp Gly Asp Tyr Gln Thr Gly Arg Pro 210 215 220		
10	Leu Gln Ser Val Gly Cys Leu Leu Pro Glu Arg Cys Thr Pro Glu Gln 225 230 235 240		
	Leu Ala Val Met Leu Glu Ala Ala Ala Asp Gly Thr Gly His Val Ala 245 250 255		
15	Ala Thr Asp Arg Tyr Arg Met Phe Ser Ala Ala Ser Gly Ser Tyr Pro 260 265 270		
20	Cys Arg Ala Gly Tyr Cys Ser Leu Ala Asp Arg Pro Glu Thr Ala Ala 275 280 285		
25	Gly Arg Arg Arg Ile Phe Phe Pro Ala Pro Ala Arg Pro Asp Val Gln 290 295 300		
	Pro Ala Ala Cys Arg Arg Ala Gly Gly Gln His Leu Met Gln Trp Leu 305 310 315 320		
30	Pro Ser Pro Val Trp Ala Gly Val Thr Val Ile Thr Arg Ala Gly Ala 325 330 335		
35	Arg Trp Val Phe Leu Trp Leu Arg Thr Ala Leu Met Ser Ala Val Cys 340 345 350		
40	Val Leu Val Ile Trp Gly Ala Gly Met Thr Thr Ser Phe Phe Ala Asn 355 360 365		
	Arg Ala Leu Val Gln Glu Thr Gly Ile Gln Thr Ala Arg Ala Leu Asp 370 375 380		
45	Thr Arg Leu Pro Leu Ala Glu Gln Leu Val Ala Leu His Thr Leu Gln 385 390 395 400		
50	Gly Glu Leu Glu Arg Leu Gln Tyr Arg Ile Arg Glu Gly Ala Pro Trp 405 410 415		
55	Tyr Gln Arg Phe Gly Leu Glu Arg Asn Gln Gln Leu Leu Ala Ala Ala 420 425 430		

EP 1 342 784 A1

5 Phe Pro Gly Tyr Ala Gln Ala Ala Asn Arg Leu Val Arg Asp Val Ala  
435 440 445

10 Val Asp His Leu Gln Gln Gln Leu Asn Ala Phe Val Ala Leu Pro Pro  
450 455 460

15 Lys Ala Leu Leu Met Thr Ser Arg Pro Glu Lys Ala Asp Ala Ala Phe  
485 490 495

20 Phe Ser Thr Thr Leu Met Ala Asp Gly Leu Arg Tyr Glu Asn Ile Pro  
500 505 510

25 Glu Gly Val Arg Gln Ser Val Leu Pro Ser Leu Leu Thr Phe Trp Thr  
515 520 525

30 Ala Asn Leu Pro Glu His Pro Gln Trp Lys Thr Ser Pro Pro Pro Glu  
530 535 540

35 Leu Thr Gly Ala Val Arg Lys Ile Leu Leu Arg Gln Ile Gly Val Arg  
545 550 555 560

Asn Ala Glu Asn Thr Leu Tyr Gln Asn Val Leu Gln Gln Val Ser Arg  
565 570 575

40 Asn Tyr Ala Asp Met Thr Leu Ala Asp Met Thr Gly Asp Thr Leu Thr  
580 585 590

Glu Ser Leu Phe Ser Thr Glu Gln Thr Val Pro Gly Met Phe Thr Arg  
595 600 605

45 Gln Ala Trp Glu Gly Gln Val Arg Glu Ala Ile Glu Gln Val Val Thr  
610 615 620

50 Ala Arg Arg Glu Glu Ile Asp Trp Val Leu Ser Asp Arg Gln Gln Asp  
625 630 635 640

55 Thr Ser Ala Asp Ile Ser Pro Asp Thr Leu Arg Asn Arg Leu Thr Ser  
645 650 655

# EP 1 342 784 A1

Arg Tyr Phe Thr Asp Phe Ala Gly Ser Trp Leu Ala Phe Leu Asn Ser  
 660 665 670  
 5  
 Ile His Trp Lys Lys Glu Asp Ser Leu Ser Gly Ile Leu Asp Gln Leu  
 675 680 685  
 10  
 Thr Leu Met Ala Asp Ala Arg Gln Ser Pro Leu Ile Ala Leu Thr Asp  
 690 695 700  
 15  
 Thr Leu Ala Trp Gln Ala Ala Thr Gly Arg Glu Asn Arg Gly Leu Ser  
 705 710 715 720  
 Asp Ser Leu Ala Lys Ser Ala Gln Glu Leu Phe Asn Gly Lys Glu Lys  
 725 730 735  
 20  
 Thr Pro Gln Gln Ser Arg Glu Gly Asp Asp Val Pro Val Gly Pro Leu  
 740 745 750  
 25  
 Asp Lys Thr Phe Thr Pro Leu Leu Arg Leu Leu Gly Asp Lys Ala Gly  
 755 760 765  
 30  
 Gly Gly Asp Ser Gln Leu Ser Leu Gln Thr Tyr Leu Thr Arg Val Thr  
 770 775 780  
 Arg Val Arg Leu Lys Leu Gln Gln Val Thr Asn Ala Pro Asp Pro Gln  
 785 790 795 800  
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 Glu Met Thr Gln Gln Leu Ala Gln Thr Val Leu Gln Gly Lys Thr Val  
 805 810 815  
 40  
 Asp Leu Thr Asp Thr Arg Asp Tyr Gly Arg Leu Ile Ala Ala Ser Leu  
 820 825 830  
 45  
 Gly Glu Glu Trp Ser Gly Phe Gly Gln Ala Leu Phe Val Arg Pro Val  
 835 840 845  
 Glu Gln Ser Trp Arg Gln Val Leu Thr Pro Ala Ala Asp Ser Leu Asn  
 850 855 860  
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 Arg Gln Trp Gln Arg Ala Ile Val Ser His Trp Asn Gln Asp Phe Ala  
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EP 1 342 784 A1

Gly Arg Tyr Pro Phe Lys Ala Ser Gln Asn Asp Ala Ser Leu Pro Leu  
885 890 895

5 Leu Ala Gln Tyr Leu Arg Asp Asp Gly Arg Ile Asn Leu Phe Ile Ala  
900 905 910

10 Ala Asn Leu Ser Gly Val Leu Lys Arg Glu Gly Arg Tyr Trp Val Ala  
915 920 925

15 Asp Ala Met Asn Thr Gln Gly Leu Thr Val Asn Pro Asp Phe Ile Arg  
930 935 940

Ala Leu Asn Arg Leu Arg Asp Val Ala Asp Thr Ala Phe Ala Ser Gly  
945 950 955 960

20 Asp Ala Gly Ile His Phe Glu Leu Arg Ala Lys Pro Ala Arg Asp Val  
965 970 975

25 Met Lys Thr His Leu Val Ile Asp Gly Gln Glu Leu Glu Tyr Phe Asn  
980 985 990

Gln Lys Glu Arg Trp Gln Arg Phe Asn Trp Pro Asp Glu Gln Trp Gln  
995 1000 1005

30 Pro Gly Ala Ser Leu Ser Trp Thr Ser Thr Gln Ala Met Glu Arg  
1010 1015 1020

35 Ile Leu Ala Asp Tyr Arg Gly Ser Trp Ser Leu Ile Arg Leu Leu  
1025 1030 1035

40 Glu Gln Ala Gln Val Thr Pro Val Asp Ser Ser Thr Phe Lys Val  
1040 1045 1050

45 Val Trp Lys Ala Gln Asp Gly Leu Pro Leu Asn Tyr Leu Leu Arg  
1055 1060 1065

Val Glu Gln Gly Lys Gly Pro Leu Ala Leu Leu Glu Leu Lys Asn  
1070 1075 1080

50 Phe Arg Leu Pro Gly Gln Val Phe Leu Thr Gly Lys Ser Met Lys  
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55 Asp Val Glu Glu Tyr Gly Glu Asp Ala Asp Glu

EP 1 342 784 A1

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10 Met Phe Pro Ile Arg Phe Lys Arg Pro Ala Leu Leu Cys Met Ala Met  
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15 Leu Thr Val Val Leu Ser Gly Cys Gly Leu Ile Gln Lys Val Val Asp  
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20 Glu Ser Lys Ser Val Ala Ser Ala Val Phe Tyr Lys Gln Ile Lys Ile  
 35 40 45

25 Leu His Leu Asp Phe Phe Ser Arg Ser Ala Leu Asn Thr Asp Ala Glu  
 50 55 60

30 Asp Thr Pro Leu Ser Thr Met Val His Val Trp Gln Leu Lys Thr Arg  
 65 70 75 80

35 Glu Asp Phe Asp Lys Ala Asp Tyr Asp Thr Leu Phe Met Gln Glu Glu  
 85 90 95

40 Lys Thr Leu Glu Lys Asp Val Leu Ala Lys His Thr Val Trp Val Lys  
 100 105 110

45 Pro Glu Gly Thr Ala Ser Leu Asn Val Pro Leu Asp Lys Glu Thr Gln  
 115 120 125

50 Phe Val Ala Ile Ile Gly Gln Phe Tyr His Pro Asp Glu Lys Ser Asp  
 130 135 140

55 Ser Trp Arg Leu Val Ile Lys Arg Asp Glu Leu Glu Ala Asp Lys Pro  
 145 150 155 160

Arg Ser Ile Glu Leu Met Arg Ser Asp Leu Arg Leu Leu Pro Leu Lys  
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Asp Lys

EP 1 342 784 A1

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 <211> 280  
 <212> PRT  
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Ser Leu Leu Thr Leu Ala Gly Ala Ser Leu Pro Leu Ser Gly Cys Ile  
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Ser Arg Gly Gln Glu Ser Ile Ser Glu Gly Ala Ala Phe Gly Ala Gly  
 35 40 45

Ile Leu Arg Glu Pro Gly Ala Thr Lys Lys Ala Asp Thr Lys Asp Leu  
 50 55 60

Asn Val Pro Pro Pro Val Tyr Gly Pro Pro Gln Val Ile Phe Arg Ile  
 65 70 75 80

Asp Asp Asn Arg Tyr Phe Thr Leu Glu Asn Tyr Thr His Cys Glu Asn  
 85 90 95

Gly Gln Thr Phe Tyr Asn Asn Lys Ala Lys Asn Ile His Val Lys Ile  
 100 105 110

Leu Asp Ala Ser Gly Tyr Leu Phe Lys Gly Arg Leu Phe Trp Leu Ser  
 115 120 125

Thr Arg Asp Asp Phe Leu Ala Phe Pro Ala Thr Leu Asn Thr Arg His  
 130 135 140

Ala Ser Cys Met Gly Ser Asn Lys Gly Cys Met Asn Ala Val Ile Val  
 145 150 155 160

Thr Thr Asp Gly Gly Lys Arg Arg Ser Gly Val Pro Tyr Gly Ser Tyr  
 165 170 175

Thr Gln Asn Pro Thr Gly Ala Thr Arg Asp Tyr Asp Met Leu Val Met  
 180 185 190

Asn Asp Gly Phe Tyr Leu Leu Arg Tyr Arg Gly Gly Gln Gly Arg Phe  
 195 200 205

EP 1 342 784 A1

Ser Pro Val Ile Leu Arg Trp Ile Leu Ser Thr Glu Asp Ser Ser Gly  
 210 215 220  
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 Val Val Arg Ser Glu Asp Ala Tyr Glu Leu Phe Arg Pro Gly Glu Glu  
 225 230 235 240  
 10  
 Val Pro Ser Thr Gly Phe Tyr Lys Ile Asp Leu Ser Arg Phe Tyr Pro  
 245 250 255  
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 Lys Asn Asn Val Met Glu Met Gln Cys Asp Arg Thr Leu Glu Pro Val  
 260 265 270  
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 Gln Pro Ser Glu Ser Lys Ile Gln  
 275 280  
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 Ile Gly Ala Gln Asp Glu Arg Leu Ser Thr Leu Ile His Gln Arg Met  
 35 40 45  
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 Gln Glu Ala Lys Val Pro Ala Leu Ser Val Ser Val Thr Ile Lys Gly  
 50 55 60  
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 Val Arg Gln Arg Phe Val Tyr Gly Val Ala Asp Val Ala Ser Gln Lys  
 65 70 75 80  
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 Ala Asn Thr Leu Asp Thr Val Tyr Glu Leu Gly Ser Met Ser Lys Ala  
 85 90 95  
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 Phe Thr Gly Leu Val Val Gln Ile Leu Ile Gln Glu Gly Arg Leu Arg  
 100 105 110  
 Gln Gly Asp Asp Ile Ile Thr Tyr Leu Pro Glu Met Arg Leu Asn Tyr  
 115 120 125



EP 1 342 784 A1

5 Gln Gly Lys Pro Ala Ser Leu Thr Val Ala Asp Phe Leu Tyr His Thr  
130 135 140

10 Ser Gly Leu Pro Phe Ser Thr Leu Ala Arg Leu Glu Asn Pro Met Pro  
145 150 155 160

15 Gly Ser Ala Val Ala Gln Gln Leu Arg Asn Glu Asn Leu Leu Phe Ala  
165 170 175

20 Pro Gly Ala Lys Phe Ser Tyr Ala Ser Ala Asn Tyr Asp Val Leu Gly  
180 185 190

25 Ala Val Ile Glu Asn Val Thr Gly Lys Thr Phe Thr Glu Val Ile Ala  
195 200 205

30 Glu Arg Leu Thr Gln Pro Leu Gly Met Ser Ala Thr Val Ala Val Lys  
210 215 220

35 Gly Asp Glu Ile Ile Val Asn Lys Ala Ser Gly Tyr Lys Leu Gly Phe  
225 230 235 240

40 Gly Lys Pro Val Leu Phe His Ala Pro Leu Ala Arg Asn His Val Pro  
245 250 255

45 Ala Ala Tyr Ile His Ser Thr Leu Pro Asp Met Glu Ile Trp Ile Asp  
260 265 270

50 Ala Trp Leu His Arg Lys Ala Leu Pro Ala Thr Leu Arg Glu Ala Met  
275 280 285

55 Ser Asn Ser Trp Arg Gly Asn Ser Asp Val Pro Leu Ala Ala Asp Asn  
290 295 300

Arg Ile Leu Tyr Ala Ser Gly Trp Phe Ile Asp Gln Asn Gln Gly Pro  
305 310 315 320

Tyr Ile Ser His Gly Gly Gln Asn Pro Asn Phe Ser Ser Cys Ile Ala  
325 330 335

Leu Arg Pro Asp Gln Gln Ile Gly Ile Val Ala Leu Ala Asn Met Asn  
340 345 350

# EP 1 342 784 A1

Ser Asn Leu Ile Leu Gln Leu Cys Ala Asp Ile Asp Asn Tyr Leu Arg  
 355 360 365  
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 Ile Gly Lys Tyr Ala Asp Gly Ala Gly Asp Ala Ile Thr Ala Thr Asp  
 370 375 380  
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 Thr Leu Phe Val Tyr Leu Thr Leu Leu Leu Cys Phe Trp Gly Ala Val  
 385 390 395 400  
 15  
 Val Val Val Arg Gly Ala Phe Arg Val Tyr Arg Ala Thr Ala His Gly  
 405 410 415  
 Pro Gly Lys Gln Gln Arg Leu Arg Leu Arg Val Arg Asp Tyr Ile Ile  
 420 425 430  
 20  
 Ala Leu Ala Val Pro Gly Leu Val Ala Ala Met Leu Tyr Val Ala Pro  
 435 440 445  
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 Gly Ile Leu Ser Pro Gly Leu Asp Trp Arg Phe Ile Leu Val Trp Gly  
 450 455 460  
 Pro Ser Ser Val Leu Ala Ile Pro Phe Gly Ile Ile Leu Leu Ala Phe  
 465 470 475 480  
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 Val Leu Thr Leu Asn His Gln Ile Lys Arg Ile Leu Leu His Asn Lys  
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 Glu Trp Asp Asp Glu  
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 Ala Val Ile Ser Ser Gly Tyr Ala Ser Ser Asp Lys Lys Glu Asp Thr  
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 35 40 45  
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EP 1 342 784 A1

5 Ala Ser Val Ser Val Ile Thr Ser Glu Gln Leu Gln Lys Lys Pro Val  
50 55 60

10 Ser Asp Leu Val Asp Ala Val Lys Asp Val Glu Gly Ile Ser Ile Thr  
65 70 75 80

15 Gly Gly Asn Glu Lys Pro Asp Ile Ser Ile Arg Gly Leu Ser Gly Asp  
85 90 95

20 Tyr Thr Leu Ile Leu Val Asp Gly Arg Arg Gln Ser Gly Arg Glu Ser  
100 105 110

25 Arg Pro Asn Gly Ser Gly Gly Phe Glu Ala Gly Phe Ile Pro Pro Val  
115 120 125

30 Glu Ala Ile Glu Arg Ile Glu Val Ile Arg Gly Pro Met Ser Ser Leu  
130 135 140

35 Tyr Gly Ser Asp Ala Ile Gly Gly Val Ile Asn Ile Ile Thr Lys Pro  
145 150 155 160

40 Val Asn Asn Gln Thr Trp Asp Gly Val Leu Gly Leu Gly Gly Ile Ile  
165 170 175

45 Gln Glu His Gly Lys Phe Gly Asn Ser Thr Thr Asn Asp Phe Tyr Leu  
180 185 190

50 Ser Gly Pro Leu Ile Lys Asp Lys Leu Gly Leu Gln Leu Tyr Gly Gly  
195 200 205

55 Met Asn Tyr Arg Lys Glu Asp Ser Ile Ser Gln Gly Thr Pro Ala Lys  
210 215 220

60 Asp Asn Lys Asn Ile Thr Ala Thr Leu Gln Phe Thr Pro Thr Glu Ser  
225 230 235 240

65 Gln Lys Phe Val Phe Glu Tyr Gly Lys Asn Asn Gln Val His Thr Leu  
245 250 255

70 Thr Pro Gly Glu Ser Leu Asp Ala Trp Thr Met Arg Gly Asn Leu Lys  
260 265 270

EP 1 342 784 A1

5 Gln Pro Asn Ser Lys Arg Glu Thr His Asn Ser Arg Ser His Trp Val  
275 280 285

10 Ala Ala Trp Asn Ala Gln Gly Glu Ile Leu His Pro Glu Ile Ala Val  
290 295 300

15 Tyr Gln Glu Lys Val Ile Arg Glu Val Lys Ser Gly Lys Lys Asp Lys  
305 310 315 320

20 Tyr Asn His Trp Asp Leu Asn Tyr Glu Ser Arg Lys Pro Glu Ile Thr  
325 330 335

25 Asn Thr Ile Ile Asp Ala Lys Val Thr Ala Phe Leu Pro Glu Asn Val  
340 345 350

30 Leu Thr Ile Gly Gly Gln Phe Gln His Ala Glu Leu Arg Asp Asp Ser  
355 360 365

35 Ala Thr Gly Lys Lys Thr Thr Glu Thr Gln Ser Val Ser Ile Lys Gln  
370 375 380

40 Lys Ala Val Phe Ile Glu Asn Glu Tyr Ala Ala Thr Asp Ser Leu Ala  
385 390 395 400

45 Leu Thr Gly Gly Leu Arg Leu Asp Asn His Glu Ile Tyr Gly Ser Tyr  
405 410 415

50 Trp Asn Pro Arg Leu Tyr Ala Val Tyr Asn Leu Thr Asp Asn Leu Thr  
420 425 430

55 Leu Lys Gly Gly Ile Ala Lys Ala Phe Arg Ala Pro Ser Ile Arg Glu  
435 440 445

Val Ser Pro Gly Phe Gly Thr Leu Thr Gln Gly Gly Ala Ser Ile Met  
450 455 460

Tyr Gly Asn Arg Asp Leu Lys Pro Glu Thr Ser Val Thr Glu Glu Ile  
465 470 475 480

Gly Ile Ile Tyr Ser Asn Asp Ser Gly Phe Ser Ala Ser Ala Thr Leu  
485 490 495

EP 1 342 784 A1

Phe Asn Thr Asp Phe Lys Asn Lys Leu Thr Ser Tyr Asp Ile Gly Thr  
500 505 510

5 Lys Asp Pro Val Thr Gly Leu Asn Thr Phe Ile Tyr Asp Asn Val Gly  
515 520 525

10 Glu Ala Asn Ile Arg Gly Val Glu Leu Ala Thr Gln Ile Pro Val Tyr  
530 535 540

Asp Lys Trp His Val Ser Ala Asn Tyr Thr Phe Thr Asp Ser Arg Arg  
545 550 555 560

15 Lys Ser Asp Asp Glu Ser Leu Asn Gly Lys Ser Leu Lys Gly Glu Pro  
565 570 575

20 Leu Glu Arg Thr Pro Arg His Ala Ala Asn Ala Lys Leu Glu Trp Asp  
580 585 590

25 Tyr Thr Gln Asp Ile Thr Phe Tyr Ser Ser Leu Asn Tyr Thr Gly Lys  
595 600 605

Gln Ile Trp Ala Ala Gln Arg Asn Gly Ala Lys Val Pro Arg Val Arg  
610 615 620

30 Asn Gly Phe Thr Ser Met Asp Ile Gly Leu Asn Tyr Gln Ile Leu Pro  
625 630 635 640

35 Asp Thr Leu Ile Asn Phe Ala Val Leu Asn Val Thr Asp Arg Lys Ser  
645 650 655

Glu Asp Ile Asp Thr Ile Asp Gly Asn Trp Gln Val Asp Glu Gly Arg  
660 665 670

40 Arg Tyr Trp Ala Asn Val Arg Val Ser Phe  
675 680

45 <210> 41  
<211> 164  
<212> PRT  
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50 <400> 41

Met Gly Phe Arg Lys Thr Ile Ile Thr Ser Val Gly Leu Ile Phe Ile  
1 5 10 15

55

EP 1 342 784 A1

Ser Phe Ser Phe Val Ala Lys Cys Ser Gln Leu Lys Asn Leu Asn Asn  
 20 25 30  
 5  
 Tyr Ser Val Met Leu Cys Gly Lys Val Ser Asn Asn Ile Leu Asp Asp  
 35 40 45  
 10  
 Ile Gly Gly Tyr Lys Glu Arg Asn Ile Leu Met Leu Arg Ala Ile Lys  
 50 55 60  
 15  
 Lys Ile Ile Ile Met Thr Ile Val Asn Ile Ile Phe Phe Tyr Ser Phe  
 65 70 75 80  
 Gln Ser Thr Ala Asp Glu Met Val Leu Ile Lys Lys Tyr Gly Phe Gly  
 85 90 95  
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 Leu Glu Arg Asp Ile Lys Gly Arg Pro Leu Ile Tyr Pro Ile Glu Asn  
 100 105 110  
 25  
 Tyr Asp Glu Cys Lys Lys Lys Cys Asn His Met Asn Tyr Ile Ala Asp  
 115 120 125  
 30  
 Val Asn Ala Gln Leu Ala Met Ser Lys Lys Asn Asn Arg Ile Phe Ala  
 130 135 140  
 Asn Ile Thr Phe Thr Asn Asn Ser Ser Thr Thr Tyr Phe Phe Leu Asn  
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 Ile Ile Tyr Leu  
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 Ile Ser Val Ile Leu Leu Ser Gly Gly Ile Met Gly Thr Gly Leu Tyr  
 20 25 30  
 55  
 Ser Ser Asp Asn His Gln Lys Ile Arg Ser Arg Phe Asn Ile Gln Glu  
 35 40 45

5 Ser Tyr Cys Ala Ile Lys Thr Asn Gly Val Leu Gly Phe Ser Asn Arg  
 50 55 60

10 Lys Asp Val Leu Arg Glu Asn Gly Asp Ser Thr Gly Thr Thr Ser Ser  
 65 70 75 80

15 Ser Thr Asn Ala Met Met Leu Met Glu Asn Gly Glu Asn Glu Ile Ser  
 85 90 95

20 Leu Glu Ile Gly Ala Leu Arg Trp Phe Ser Asp Lys Pro Ala Ser Thr  
 100 105 110

25 Glu Glu Arg Gly His Phe Ser Gln Lys Ala Gly Cys Ser Leu Asp Leu  
 115 120 125

30 Val Arg Phe Val Lys Gln Glu Glu Thr Ile Leu Ser Ser Ile Lys Val  
 130 135 140

35 Thr Ile Asn Gln Gln Gly Ile Pro Glu Ala Gln Pro Asp Ser Met His  
 145 150 155 160

40 Pro Val Ile Arg Lys Glu Ile Leu Ala Glu Gln Ala Glu Pro Gly Phe  
 165 170 175

45 Ile Asp Pro Asp Tyr Phe Asn Glu Thr Tyr Phe Pro Lys Gly Met Lys  
 180 185 190

50 Val Tyr Gln Phe Thr Gln Lys Val Ser Val Ala Gly Leu Pro Asp Gly  
 195 200 205

55 Pro Gly Arg Ser Thr Pro Phe Thr Gly Ala  
 210 215

<210> 43  
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 <212> PRT  
 <213> Escherichia coli  
 <400> 43

Met His Gln Pro Pro Val Arg Phe Thr Tyr Arg Leu Leu Ser Tyr Leu  
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Val Ser Ala Ile Ile Ala Gly Gln Pro Leu Leu Pro Ala Val Gly Ala

EP 1 342 784 A1

	20	25	30
5	Val Ile Thr Pro Gln Asn Gly 35	Ala Gly Met Asp Lys Ala Ala Asn Gly 40	
10	Val Pro Val Val Asn Ile Ala Thr Pro Asn Gly Ala Gly Ile Ser His 50	55	60
15	Asn Arg Phe Thr Asp Tyr Asn Val Gly Lys Glu Gly Leu Ile Leu Asn 65	70	75 80
20	Asn Ala Thr Gly Lys Leu Asn Pro Thr Gln Leu Gly Gly Leu Ile Gln 85	90	95
25	Asn Asn Pro Asn Leu Lys Ala Gly Gly Glu Ala Lys Gly Ile Ile Asn 100	105	110
30	Glu Val Thr Gly Gly Lys Arg Ser Leu Leu Gln Gly Tyr Thr Glu Val 115	120	125
35	Ala Gly Lys Ala Ala Asn Val Met Val Ala Asn Pro Tyr Gly Ile Thr 130	135	140
40	Cys Asp Gly Cys Gly Phe Ile Asn Thr Pro His Ala Thr Leu Thr Thr 145	150	155 160
45	Gly Lys Pro Val Met Asn Ala Asp Gly Ser Leu Gln Ala Leu Glu Val 165	170	175
50	Thr Glu Gly Ser Ile Thr Ile Asn Gly Ala Gly Leu Asp Gly Thr Arg 180	185	190
55	Ser Asp Ala Val Ser Ile Ile Ala Arg Ala Thr Glu Val Asn Ala Ala 195	200	205
	Leu His Ala Lys Asp Leu Thr Val Thr Ala Gly Ala Asn Arg Val Thr 210	215	220
	Ala Asp Gly Arg Val Arg Ala Leu Lys Gly Glu Gly Asp Val Pro Lys 225	230	235 240
	Val Ala Val Asp Thr Gly Ala Leu Gly Gly Met Tyr Ala Arg Arg Ile 245	250	255



EP 1 342 784 A1

5 His Leu Thr Ser Thr Glu Ser Gly Val Gly Val Asn Leu Gly Asn Leu  
250 265 270

10 Tyr Ala Arg Asp Gly Asp Ile Thr Leu Asp Ala Ser Gly Arg Leu Thr  
275 280 285

15 Val Asn Asn Ser Leu Ala Thr Gly Ala Val Thr Ala Lys Gly Gln Gly  
290 295 300

20 Ser Arg Arg Asp Ile Val Leu Ser Asn Gly Thr Leu Asn Ser Asp Lys  
325 330 335

25 Asp Leu Ser Leu Thr Ala Gly Gly Arg Ile Thr Gln Gln Asn Glu Lys  
340 345 350

30 Leu Thr Ala Gly Arg Asp Val Thr Leu Ala Ala Lys Asn Ile Thr Gln  
355 360 365

35 Asp Thr Ala Ser Gln Ile Asn Ala Ala Arg Asp Ile Val Thr Val Ala  
370 375 380

40 Ser Asp Thr Leu Thr Thr Gln Gly Gln Ile Thr Ala Gly Gln Asn Leu  
385 390 395 400

45 Thr Ala Ser Ala Thr Thr Leu Thr Gln Asp Gly Ile Leu Leu Ala Lys  
405 410 415

50 Ser His Ala Gly Leu Asn Ala Gly Thr Leu Asn Asn Ser Gly Ala Val  
420 425 430

55 Gln Gly Ala Thr Leu Thr Leu Gly Ser Thr Thr Leu Ser Asn Ser Gly  
435 440 445

Ser Leu Leu Ser Gly Gly Pro Leu Thr Met Asn Thr Arg Asp Phe Thr  
450 455 460

Gln Ser Gly Arg Thr Gly Ala Lys Gly Lys Val Asp Ile Met Ala Ser  
465 470 475 480

EP 1 342 784 A1

5 Gly Lys Leu Thr Ser Thr Gly Leu Leu Val Thr Met His Leu Val Leu  
485 490 495

10 Lys Ala Gln Asp Val Thr Gln Asn Gly Val Leu Ser Gly Gly Lys Gly  
500 505 510

15 Leu Thr Val Ser Ala Thr Ser Ser Gly Lys Lys Ser Val Thr His Ser  
515 520 525

20 Asp Ala Ala Met Thr Leu Asn Val Thr Thr Val Ala Leu Asp Gly Glu  
530 535 540

25 Thr Ser Ala Gly Asp Thr Leu Arg Val Gln Ala Asp Lys Leu Ser Thr  
545 550 555 560

30 Ala Ala Gly Ala Gln Leu Gln Ser Gly Lys Asn Leu Ser Ile Asn Ala  
565 570 575

35 Arg Asp Ala Arg Leu Ala Gly Thr Gln Ala Ala Gln Gln Thr Met Val  
580 585 590

40 Val Asn Ala Ser Glu Lys Leu Thr His Ser Gly Lys Ser Ser Ala Pro  
595 600 605

45 Ser Leu Ser Leu Ser Ala Pro Glu Leu Thr Ser Ser Gly Val Leu Val  
610 615 620

50 Gly Ser Ala Leu Asn Thr Gln Ser Gln Thr Leu Thr Asn Ser Gly Leu  
625 630 635 640

55 Leu Gln Gly Glu Ala Ser Leu Thr Val Asn Thr Gln Arg Leu Asp Asn  
645 650 655

60 Gln Gln Asn Gly Thr Leu Tyr Ser Ala Ala Asp Leu Thr Leu Asp Ile  
660 665 670

65 Pro Asp Ile Arg Asn Ser Gly Leu Ile Thr Gly Asp Asn Gly Leu Met  
675 680 685

70 Leu Asn Ala Val Ser Leu Ser Asn Pro Gly Lys Ile Ile Ala Asp Thr  
690 695 700

EP 1 342 784 A1

Leu Ser Val Arg Ala Thr Thr Leu Asp Gly Asp Gly Leu Leu Gln Gly  
705 710 715 720

5 Ala Gly Ala Leu Ala Leu Ala Gly Asp Thr Leu Ser Gln Gly Ser His  
725 730 735

10 Gly Arg Trp Leu Thr Ala Asp Asp Leu Ser Leu Arg Gly Lys Thr Leu  
740 745 750

15 Asn Thr Ala Gly Thr Thr Gln Gly Gln Asn Ile Thr Val Gln Ala Asp  
755 760 765

Arg Trp Ala Asn Ser Gly Ser Val Leu Ala Thr Gly Asn Leu Thr Ala  
770 775 780

20 Ser Ala Thr Gly Gln Leu Thr Ser Thr Gly Asp Ile Met Ser Gln Gly  
785 790 795 800

25 Asp Thr Thr Leu Lys Ala Ala Thr Thr Asp Asn Arg Gly Ser Leu Leu  
805 810 815

Ser Ala Gly Thr Leu Ser Leu Asp Gly Asn Ser Leu Asp Asn Arg Gly  
820 825 830

30 Thr Val Gln Gly Asn His Val Thr Ile Arg Gln Asn Ser Val Thr Asn  
835 840 845

35 Ser Gly Thr Leu Thr Gly Ile Ala Ala Leu Thr Leu Ala Ala Arg Met  
850 855 860

40 Ala Ser Pro Gln Pro Ala Leu Met Asn Asn Gly Gly Ser Leu Leu Thr  
865 870 875 880

Ser Gly Asp Leu Thr Ile Thr Ala Gly Ser Ile Thr Ser Ser Gly His  
885 890 895

45 Trp Gln Gly Lys Arg Val Leu Ile Thr Ala Asp Ser Leu Ala Asn Ser  
900 905 910

50 Gly Ala Ile Gln Ala Ala Asp Ser Leu Thr Ala Arg Leu Thr Gly Glu  
915 920 925

55 Leu Val Ser Thr Ala Gly Ser Lys Val Thr Ser Asn Gly Glu Met Ala

EP 1 342 784 A1

	930		935		940	
5	Leu Ser Ala Leu Asn Leu Ser Asn Ser Gly Gln Trp Ile Ala Lys Asn					
	945		950		955	960
	Leu Thr Leu Lys Ala Asn Ser Leu Thr Ser Ala Gly Asp Ile Thr Gly					
10		965		970		975
	Val Asp Thr Leu Thr Leu Thr Val Asn Gln Thr Leu Asn Asn Gln Ala					
		980		985		990
15	Asn Gly Lys Leu Leu Ser Ala Gly Val Leu Thr Leu Lys Ala Asp Ser					
		995		1000		1005
	Val Thr Asn Asp Gly Gln Leu Gln Gly Asn Val Thr Thr Ile Thr					
20		1010		1015		1020
	Ala Gly Gln Leu Thr Asn Gly Gly His Leu Gln Gly Glu Thr Leu					
25		1025		1030		1035
	Thr Leu Thr Ala Ser Gly Gly Val Asn Asn Arg Ser Gly Gly Val					
		1040		1045		1050
30	Leu Met Ser Arg Asn Ala Leu Asn Val Ser Thr Ala Thr Leu Ser					
		1055		1060		1065
	Asn Gln Ser Thr Ile Gln Gly Gly Gly Gly Val Ser Leu Asn Ala					
35		1070		1075		1080
	Thr Asp Arg Leu Gln Asn Asp Gly Lys Ile Leu Ser Gly Ser Asn					
40		1085		1090		1095
	Leu Thr Leu Thr Ala Gln Val Leu Ala Asn Thr Gly Ser Gly Leu					
		1100		1105		1110
45	Val Gln Ala Ala Thr Leu Leu Leu Asp Val Val Asn Thr Val Asn					
		1115		1120		1125
	Gly Gly Arg Val Leu Ala Thr Gly Ser Asp Val Lys Gly Thr Thr					
50		1130		1135		1140
	Leu Asn Asn Thr Gly Thr Leu Gln Gly Ala Thr Leu Val Asn Tyr					
		1145		1150		1155
55						

EP 1 342 784 A1

5 His Thr Phe Ser Ser Gly Thr Leu Leu Gly Thr Ser Gly Leu Gly  
1160 1165 1170

Val Lys Gly Ser Ser Leu Leu Gln Asn Gly Thr Gly Arg Leu Tyr  
1175 1180 1185

10 Ser Ala Gly Asn Leu Leu Leu Asp Ala Gln Asp Phe Ser Gly Gln  
1190 1195 1200

15 Gly Gln Val Val Ala Thr Gly Asp Val Thr Leu Lys Leu Ile Ala  
1205 1210 1215

Ala Leu Thr Asn His Gly Thr Leu Ala Ala Gly Lys Thr Leu Ser  
1220 1225 1230

20 Val Thr Ser Gln Asn Ala Ile Thr Asn Gly Gly Val Met Gln Gly  
1235 1240 1245

25 Asp Ala Met Val Leu Gly Ala Gly Glu Ala Phe Thr Asn Asn Gly  
1250 1255 1260

30 Leu Thr Ala Gly Lys Gly Asn Ser Val Phe Ser Ala Gln Arg Leu  
1265 1270 1275

Phe Leu Asn Ala Pro Gly Ser Leu Gln Gly Gly Gly Asp Val Ser  
1280 1285 1290

35 Leu Asn Ser Arg Ser Asp Ile Thr Ile Ser Gly Phe Thr Gly Thr  
1295 1300 1305

40 Ala Gly Ser Leu Thr Met Asn Val Ala Gly Thr Leu Leu Asn Ser  
1310 1315 1320

45 Ala Leu Ile Tyr Ala Gly Asn Asn Leu Lys Leu Phe Thr Asp Arg  
1325 1330 1335

Leu His Asn Gln His Gly Asp Ile Leu Ala Gly Asn Ser Leu Trp  
1340 1345 1350

50 Val Gln Lys Asp Ala Ser Gly Gly Ala Asn Thr Glu Ile Ile Asn  
1355 1360 1365

55

# EP 1 342 784 A1

Asn Ser Gly Asn Ile Glu Thr His Gln Gly Asp Ile Val Val Arg  
 1370 1375 1380  
 5  
 Thr Gly His Leu Leu Asn Gln Arg Glu Gly Phe Ser Ala Thr Thr  
 1385 1390 1395  
 10  
 Thr Thr Arg Thr Asn Pro Ser Ser Ile Gln Gly Met Gly Asn Ala  
 1400 1405 1410  
 15  
 Leu Val Asp Ile Pro Leu Ser Leu Leu Pro Asp Gly Ser Tyr Gly  
 1415 1420 1425  
 Tyr Phe Thr Arg Glu Val Glu Asn Gln His Gly Thr Pro Cys Asn  
 1430 1435 1440  
 20  
 Gly His Gly Ala Cys Asn Ile Thr Met Asp Thr Leu Tyr Tyr Tyr  
 1445 1450 1455  
 25  
 Ala Pro Phe Ala Asp Ser Ala Thr Gln Arg Phe Leu Ser Ser Gln  
 1460 1465 1470  
 30  
 Asn Ile Thr Thr Val Thr Gly Ala Asp Asn Pro Ala Gly Arg Ile  
 1475 1480 1485  
 Ala Ser Gly Arg Asn Leu Ser Ala Glu Ala Glu Arg Leu Glu Asn  
 1490 1495 1500  
 35  
 Arg Ala Ser Phe Ile Leu Ala Asn Gly Asp Ile Ala Leu Ser Gly  
 1505 1510 1515  
 40  
 Arg Glu Leu Ser Asn Gln Ser Trp Gln Thr Gly Thr Glu Asn Glu  
 1520 1525 1530  
 45  
 Tyr Leu Val Tyr Arg Tyr Asp Pro Lys Thr Phe Tyr Gly Ser Tyr  
 1535 1540 1545  
 Ala Thr Gly Ser Leu Asp Lys Leu Pro Leu Leu Ser Pro Glu Phe  
 1550 1555 1560  
 50  
 Glu Asn Asn Thr Ile Arg Phe Ser Leu Asp Gly Arg Glu Lys Asp  
 1565 1570 1575  
 55

EP 1 342 784 A1

	Tyr Thr	Pro Gly Lys Thr	Tyr Tyr Ser Val Ile	Gln Ala Gly Gly
	1580		1585	1590
5	Asp Val	Lys Thr Arg Phe Thr	Ser Ser Ile Asn Asn	Gly Thr Thr
	1595		1600	1605
10	Thr Ala	His Ala Gly Ser Val	Ser Pro Val Val Ser	Ala Pro Val
	1610		1615	1620
15	Leu Asn	Thr Leu Ser Gln Gln	Thr Gly Gly Asp Ser	Leu Thr Gln
	1625		1630	1635
20	Thr Ala	Leu Gln Gln Tyr Glu	Pro Val Val Val Gly	Ser Pro Gln
	1640		1645	1650
25	Trp His	Asp Glu Leu Ala Gly	Ala Leu Lys Asn Ile	Ala Gly Gly
	1655		1660	1665
30	Ser Pro	Leu Thr Gly Gln Thr	Gly Ile Ser Asp Asp	Trp Pro Leu
	1670		1675	1680
35	Pro Ser	Gly Asn Asn Gly Tyr	Leu Val Pro Ser Thr	Asp Pro Asp
	1685		1690	1695
40	Ser Pro	Tyr Leu Ile Thr Val	Asn Pro Lys Leu Asp	Gly Leu Gly
	1700		1705	1710
45	Gln Val	Asp Ser His Leu Phe	Ala Gly Leu Tyr Glu	Leu Leu Gly
	1715		1720	1725
50	Ala Lys	Pro Gly Gln Ala Pro	Arg Glu Thr Ala Pro	Ser Tyr Thr
	1730		1735	1740
55	Asp Glu	Lys Gln Phe Leu Gly	Ser Ser Tyr Phe Leu	Asp Arg Leu
	1745		1750	1755
60	Gly Leu	Lys Pro Glu Lys Asp	Tyr Arg Phe Leu Gly	Asp Ala Val
	1760		1765	1770
65	Phe Asp	Thr Arg Tyr Val Ser	Asn Ala Val Leu Ser	Arg Thr Gly
	1775		1780	1785
70	Ser Arg	Tyr Leu Asn Gly Leu	Gly Ser Asp Thr Glu	Gln Met Arg

EP 1 342 784 A1

	1790		1795		1800
5	Tyr Leu Met Asp Asn Ala	Ala Arg Gln Gln Lys Gly	Leu Gly Leu	1805	1810 1815
10	Glu Phe Gly Val Ala Leu Thr	Ala Glu Gln Ile Ala	Gln Leu Asp	1820	1825 1830
15	Gly Ser Ile Leu Trp Trp Glu	Ser Val Thr Ile Asn	Gly Gln Thr	1835	1840 1845
20	Val Met Val Pro Lys Leu Tyr	Leu Ser Pro Glu Asp	Ile Thr Leu	1850	1855 1860
25	His Asn Gly Ser Val Ile Ser	Gly Asn Asn Val Gln	Leu Ala Gly	1865	1870 1875
30	Gly Asn Ile Thr Asn Ser Gly	Gly Ser Ile Asn Ala	Gln Asn Asp	1880	1885 1890
35	Leu Ser Leu Asp Ser Ser Gly	Tyr Ile Asp Asn Leu	Asn Ala Gly	1895	1900 1905
40	Leu Ile Ser Ala Gly Gly Ser	Leu Asp Leu Ser Ala	Ile Gly Asp	1910	1915 1920
45	Ile Ser Asn Ile Ser Ser Val	Ile Ser Gly Lys Thr	Val Gln Leu	1925	1930 1935
50	Glu Ser Val Ser Gly Asn Ile	Ser Asn Ile Thr Arg	Arg Gln Gln	1940	1945 1950
55	Trp Asn Ala Gly Ser Asp Ser	Gln Tyr Gly Gly Val	His Leu Ser	1955	1960 1965
	Gly Thr Asp Thr Gly Pro Val	Ala Thr Ile Lys Gly	Thr Asp Ser	1970	1975 1980
	Leu Ser Leu Asp Ala Gly Lys	Asn Ile Asp Ile Thr	Gly Ala Thr	1985	1990 1995
	Val Ser Ser Gly Gly Asp Leu	Gly Met Ser Ala Gly	Asn Asp Ile	2000	2005 2010



EP 1 342 784 A1

5 Asn Ile Ala Ala Asn Leu Ile Ser Gly Ser Lys Ser Gln Ser Gly  
2015 2020 2025

10 Phe Trp His Thr Asp Asp Asn Ser Ser Ser Ser Thr Thr Ser Gln  
2030 2035 2040

15 Gly Ser Ser Ile Ser Ala Gly Gly Asn Leu Ala Met Ala Ala Gly  
2045 2050 2055

20 His Asn Leu Asp Val Thr Ala Ser Ser Val Ser Ala Gly His Ser  
2060 2065 2070

25 Ala Leu Leu Ser Cys Arg Ser Arg Pro Ser Leu Glu Cys Ser Gln  
2075 2080 2085

30 Gly Lys Ala Lys Thr Ser Arg Asn Gly Arg Ser Glu Ser His Glu  
2090 2095 2100

35 Ser His Ala Ala Val Ser Thr Val Thr Ala Gly Asp Asn Phe Leu  
2105 2110 2115

40 Leu Val Ala Gly Arg Asp Ile Ala Ser Gln Ala Ala Gly Met Ala  
2120 2125 2130

45 Ala Glu Asn Asn Val Val Ile Arg Gly Gly Arg Asp Val Asn Leu  
2135 2140 2145

50 Val Ala Glu Ser Ala Gly Ala Gly Asp Ser Tyr Thr Ser Lys Lys  
2150 2155 2160

55 Lys Lys Glu Ile Asn Glu Thr Val Arg Gln Gln Gly Thr Glu Ile  
2165 2170 2175

Ala Ser Gly Gly Asp Thr Thr Val Asn Ala Gly Arg Asp Ile Thr  
2180 2185 2190

Ala Val Ala Ser Ser Val Thr Ala Thr Gly Asn Ile Ser Val Asn  
2195 2200 2205

Ala Gly Arg Asp Val Ala Leu Thr Thr Ala Thr Glu Ser Asp Tyr  
2210 2215 2220

EP 1 342 784 A1

His Tyr Leu Glu Thr Lys Lys Lys Ser Gly Gly Phe Leu Ser Lys  
 2225 2230 2235  
 5  
 Lys Thr Thr Arg Thr Ile Ser Glu Asp Ser Ala Thr Arg. Glu Ala  
 2240 2245 2250  
 10  
 Gly Ser Leu Leu Ser Gly Asn Arg Val Thr Val Asn Ala Gly Asp  
 2255 2260 2265  
 15  
 Asn Leu Thr Val Glu Gly Ser Asp Val Val Ala Asp Arg Asp Val  
 2270 2275 2280  
 Ser Leu Ala Ala Gly Asn His Val Asp Val Leu Ala Ala Thr Ser  
 2285 2290 2295  
 20  
 Thr Asp Thr Ser Trp Arg Phe Lys Glu Thr Lys Lys Ser Gly Leu  
 2300 2305 2310  
 25  
 Met Gly Thr Gly Gly Ile Gly Phe Thr Ile Gly Ser Ser Lys Thr  
 2315 2320 2325  
 30  
 Thr His Asp Arg Arg Glu Ala Gly Thr Thr Gln Ser Gln Ser Ala  
 2330 2335 2340  
 Ser Thr Ile Gly Ser Thr Ala Gly Asn Val Ser Ile Thr Ala Gly  
 2345 2350 2355  
 35  
 Lys Gln Ala His Ile Ser Gly Ser Asp Val Ile Ala Asn Arg Asp  
 2360 2365 2370  
 40  
 Ile Ser Ile Thr Gly Asp Ser Val Val Val Asp Pro Gly His Asp  
 2375 2380 2385  
 45  
 Arg Arg Thr Val Asp Glu Lys Phe Glu Gln Lys Lys Ser Gly Leu  
 2390 2395 2400  
 Thr Val Ala Leu Ser Gly Thr Val Gly Ser Ala Ile Asn Asn Ala  
 2405 2410 2415  
 50  
 Val Thr Ser Ala Gln Glu Thr Lys Glu Ser Ser Asp Ser Arg Leu  
 2420 2425 2430  
 55

EP 1 342 784 A1

Lys Ala Leu Gln Ala Thr Lys Thr Ala Leu Ser Gly Val Gln Ala  
 2435 2440 2445  
 5  
 Gly Gln Ala Ala Thr Met Ala Ser Ala Thr Gly Asp Pro Asn Ala  
 2450 2455 2460  
 10  
 Gly Val Ser Leu Ser Leu Thr Thr Gln Lys Ser Lys Ser Gln Gln  
 2465 2470 2475  
 His Ser Glu Ser Asp Thr Val Ser Gly Ser Thr Leu Asn Ala Gly  
 2480 2485 2490  
 15  
 Asn Asn Leu Ser Val Val Ala Thr Gly Lys Asn Arg Gly Asp Asn  
 2495 2500 2505  
 20  
 Arg Gly Asp Ile Val Ile Ala Gly Ser Gln Leu Lys Ala Gly Gly  
 2510 2515 2520  
 Asn Thr Ser Leu Asp Ala Ala Asn Asp Ile Leu Leu Ser Gly Ala  
 2525 2530 2535  
 25  
 Ala Asn Thr Gln Lys Thr Thr Gly Arg Asn Ser Ser Ser Gly Gly  
 2540 2545 2550  
 30  
 Gly Val Gly Val Ser Ile Gly Ala Gly Lys Gly Ala Gly Ile Ser  
 2555 2560 2565  
 35  
 Ala Phe Ala Ser Val Asn Ala Ala Lys Gly Arg Glu Lys Gly Asn  
 2570 2575 2580  
 Gly Thr Thr Thr Asp Lys Thr Val Thr Ile Asn Ser Gly Arg Asp  
 2585 2590 2595  
 40  
 Thr Val Leu Asn Gly Ala Gln Val Asn Gly Asn Arg Ile Ile Ala  
 2600 2605 2610  
 45  
 Asp Val Gly His Asp Leu Leu Ile Ser Ser Gln Gln Asp Thr Ser  
 2615 2620 2625  
 50  
 Lys Tyr Asp Ser Lys Gln Thr Ser Val Ala Ala Gly Gly Ser Phe  
 2630 2635 2640  
 Thr Phe Gly Ser Met Thr Gly Ser Gly Tyr Ile Ala Ala Ser Arg  
 55

9

EP 1 342 784 A1

Glu Ser Trp Asp Val Asn Tyr Asp Asn Pro Lys Lys Gln Asp Lys Trp  
 115 120 125  
 5 Lys Leu Glu Leu Arg Phe Tyr Pro Asn Met Thr Tyr Lys Leu Asn Asp  
 130 135 140  
 10 Gln Leu Ser Leu Tyr Met Asn Gly Phe Val Ala Pro Val Phe Phe Lys  
 145 150 155 160  
 Thr Gln Gln Glu Ser Arg Lys Asp Asn Asn Tyr Val Lys Gly Lys Leu  
 165 170 175  
 15 Gly Ala Lys Arg Tyr Asn Asn Asp Tyr Tyr Gln Glu Leu Gln Ile Leu  
 180 185 190  
 20 Gly Val Arg Tyr Lys Phe Asn Asn Asp Asn Thr Leu Trp Ala Ser Val  
 195 200 205  
 Tyr Asn Glu Arg Lys Tyr Asn Gln His Ser Ser Lys Tyr Asp Arg Trp  
 210 215 220  
 25 Gln Leu Arg Gly Gly Tyr Asp Phe Lys Val Thr Glu Glu Phe Val Leu  
 225 230 235 240  
 30 Ser Pro Phe Ile Arg Tyr Asp Leu Ser Tyr Arg Glu Lys Asn Leu Glu  
 245 250 255  
 35 Ser Thr Ser Asn Asn Gly Leu Ser Lys Asn Asn Lys Glu Ile Arg Thr  
 260 265 270  
 40 Gly Ala Ser Phe Ser Tyr Lys Ile Ile Pro Ser Val Lys Leu Val Gly  
 275 280 285  
 Glu Ile Tyr Arg Gln Thr Thr Asn Ile Glu Asn Tyr Tyr Gly Glu His  
 290 295 300  
 45 Ser Glu Asp Lys Asn Arg Met Phe Tyr Lys Leu Gly Ile Asn Lys Thr  
 305 310 315 320  
 50 Phe  
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EP 1 342 784 A1

<211> 587  
 <212> PRT  
 <213> Escherichia coli  
 <400> 45

5

Met Gln His Arg Gln Lys Asn Ile Leu Thr Lys Thr Ser Leu Leu Ser  
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10

Arg Ala Leu Ser Val Pro Cys Cys Asp Met Phe Arg Arg Gly Ser Pro  
 20 25 30

15

Trp Ile Cys Tyr Leu Ser Leu Ser Val Phe Ser Gly Cys Phe Ile Pro  
 35 40 45

20

Ala Phe Ser Ser Pro Ala Ala Met Leu Ser Pro Gly Asp Arg Ser Ala  
 50 55 60

Ile Gln Gln Gln Gln Gln Gln Leu Leu Asp Glu Asn Gln Arg Gln Arg  
 65 70 75 80

25

Asp Ala Leu Glu Arg Pro Leu Thr Ile Thr Pro Ser Pro Glu Thr Ser  
 85 90 95

30

Ala Gly Thr Glu Gly Pro Cys Phe Thr Val Ser Ser Ile Val Val Ser  
 100 105 110

Gly Ala Thr Arg Leu Thr Ser Ala Glu Thr Asp Arg Leu Val Pro Trp  
 115 120 125

35

Val Asn Gln Cys Leu Asn Ile Thr Gly Leu Thr Ala Val Thr Asp Ala  
 130 135 140

40

Val Thr Asp Gly Tyr Ile Arg Arg Gly Tyr Ile Thr Ser Arg Ala Phe  
 145 150 155 160

45

Leu Thr Glu Gln Asp Leu Ser Gly Gly Val Leu His Ile Thr Val Met  
 165 170 175

Glu Gly Arg Leu Gln Gln Ile Arg Ala Glu Gly Ala Asp Leu Pro Ala  
 180 185 190

50

Arg Thr Leu Lys Met Val Phe Pro Gly Met Glu Gly Lys Val Leu Asn  
 195 200 205

55

EP 1 342 784 A1

Leu Arg Asp Ile Glu Gln Gly Met Glu Gln Ile Asn Arg Leu Arg Thr  
210 215 220

5 Glu Pro Val Gln Ile Glu Ile Ser Pro Gly Asp Arg Glu Gly Trp Ser  
225 230 235 240

10 Val Val Thr Leu Thr Ala Leu Pro Glu Trp Pro Val Thr Gly Ser Val  
245 250 255

15 Gly Ile Asp Asn Ser Gly Gln Lys Ser Thr Gly Thr Gly Gln Leu Asn  
260 265 270

Gly Val Leu Ser Phe Asn Asn Pro Leu Gly Leu Ala Asp Asn Trp Phe  
275 280 285

20 Val Ser Gly Gly Arg Ser Ser Asp Phe Ser Val Ser His Asp Ala Arg  
290 295 300

25 Asn Phe Ala Ala Gly Val Ser Leu Pro Tyr Gly Tyr Thr Leu Val Asp  
305 310 315 320

Tyr Thr Tyr Ser Trp Ser Asp Tyr Leu Ser Thr Ile Asp Asn Arg Gly  
325 330 335

30 Trp Arg Trp Arg Ser Thr Gly Asp Leu Gln Thr His Arg Leu Gly Leu  
340 345 350

35 Ser His Val Leu Phe Arg Asn Gly Asp Met Lys Thr Ala Leu Thr Gly  
355 360 365

40 Gly Leu Gln His Arg Ile Ile His Asn Tyr Leu Asp Asp Val Leu Leu  
370 375 380

Gln Gly Ser Ser Arg Lys Leu Thr Ser Phe Ser Val Gly Leu Asn His  
385 390 395 400

45 Thr His Lys Phe Leu Gly Gly Val Gly Thr Leu Asn Pro Val Phe Thr  
405 410 415

50 Arg Gly Met Pro Trp Phe Gly Ala Glu Ser Asp His Gly Lys Arg Gly  
420 425 430

55 Asp Leu Pro Val Asn Gln Phe Arg Lys Trp Ser Val Ser Ala Ser Phe

EP 1 342 784 A1

435 440 445

5 Gln Arg Pro Val Thr Asp Arg Val Trp Trp Leu Thr Ser Ala Tyr Ala  
450 455 460

10 Gln Trp Ser Pro Asp Arg Leu His Gly Val Glu Gln Leu Ser Leu Gly  
465 470 475 480

Gly Glu Ser Ser Val Arg Gly Phe Lys Asp Gln Tyr Ile Ser Gly Asn  
485 490 495

15 Asn Gly Gly Tyr Leu Arg Asn Glu Leu Ser Trp Ser Leu Phe Ser Leu  
500 505 510

20 Pro Tyr Val Gly Thr Val Arg Ala Val Ala Ala Leu Asp Gly Gly Trp  
515 520 525

25 Leu His Ser Asp Ser Asp Asp Pro Tyr Ser Ser Gly Thr Leu Trp Gly  
530 535 540

Ala Ala Ala Gly Leu Ser Thr Thr Ser Gly His Val Ser Gly Ser Phe  
545 550 555 560

30 Thr Ala Gly Leu Pro Leu Val Tyr Pro Asp Trp Leu Ala Pro Asp His  
565 570 575

35 Leu Thr Val Tyr Trp Arg Val Ala Val Ala Phe  
580 585

40 <210> 46  
<211> 744  
<212> PRT  
<213> Escherichia coli  
<400> 46

45 Met Asn Lys His Thr Leu Leu Leu Thr Val Leu Phe Leu Asn Leu Ile  
1 5 10 15

Cys Thr Pro Val Phe Ala Gln Asn Trp Gln Val Ala Thr Phe Gly Gln  
20 25 30

50 Ser Thr Asp Leu Asn Phe Ser Ser Leu Ile Asp Ser Ala Lys Ile Gly  
35 40 45

55



EP 1 342 784 A1

Arg Asn Asn Ala Trp Leu Ala Gly Asn Asn Asn Phe Leu Glu Ala Gly  
50 55 60

5 Lys Phe Tyr Thr Leu Pro Thr Asp Phe Phe Ile Glu Ser Arg Gly Gly  
65 70 75 80

10 Lys Ile Ala Asn Ser His Asp Gly Met Thr Val Phe Tyr Thr Ile Val  
85 90 95

Pro Val Thr Gln Thr Phe Arg Leu Glu Ala Asp Leu Thr Leu Glu Gln  
100 105 110

15 Ile Gly Pro Glu Val Asn Gly Lys Ser Pro Ala Gly Gln Glu Gly Ala  
115 120 125

20 Gly Leu Phe Val Arg Asp Ile Ile Gly Pro Gln Arg Gln Glu Pro Gln  
130 135 140

25 Ser Ala Gly Thr Glu Glu Tyr Pro Gln Ala Ser Asn Ile Leu Met Asn  
145 150 155 160

Ala Phe Ile Thr Gln Asn Lys Lys Asn Asp Asn Leu Val Gln Ile Thr  
165 170 175

30 Ser Ile Val Arg Glu Gly Val Ile Lys Thr Trp Gly Asn Glu Gly Ile  
180 185 190

35 Thr Ile Lys Lys Gln Pro Ile Ile Glu Asn Ile Asn Phe Thr Gln Lys  
195 200 205

40 Arg Asn Ile His Met Thr Ile Glu Arg Leu Pro Glu Lys Phe Ile Leu  
210 215 220

Thr Ala Phe Asp Thr Asp Arg Lys Glu Asn Gln Ser Trp Gln Phe Ser  
225 230 235 240

45 Asp Tyr Ser Gly Phe Met Asn Gln Leu Asp Asn Asn Ser Leu Ala Ile  
245 250 255

50 Gly Phe Phe Ala Ala Arg Asn Ala Lys Leu Arg Val Lys Asn Ala Ser  
260 265 270

Phe Lys Pro Gly Lys Pro Leu Val Asp Tyr Lys Gln Leu Thr Ser Arg

55

EP 1 342 784 A1

	275		280		285
5	Gln Phe Ser Arg Val Arg His Lys Ala Pro Glu Leu Phe Leu Ala Ser				
	290		295		300
10	Pro Gln Ser Val Val Arg Asn Ser Thr Thr Leu Gln Phe Leu Ala Asn				
	305		310		315 320
15	Gln Ala Gly Ile Val Ser Ile Asp Asn Asp Lys Gln Thr Lys Gln Val				
		325		330	335
20	Gln Ala Gly Glu Leu Val Gln Phe Pro Val Thr Leu Gln Lys Lys His				
		340		345	350
25	Asn Asp Phe Thr Val Asn Phe Asn Val Asp Gly Asn Ile Ser Lys Lys				
		355		360	365
30	Ala Ile Arg Ile Glu Gln Val Lys Ser Asn Leu Thr Asp Pro Tyr Glu				
		370		375	380
35	Ile Tyr Val Cys Ser Asp Cys Arg Gln Gly Ala Arg Gly Ser Lys Asn				
		385		390	395 400
40	Asp Pro Val Asp Leu Gln Thr Ala Val Lys Phe Val Ala Pro Gly Gly				
		405		410	415
45	Asn Ile Tyr Leu Asn Asp Gly Gln Tyr His Gly Ile Thr Leu Asp Arg				
		420		425	430
50	Glu Leu Ser Gly Ile Pro Gly Lys Tyr Lys Thr Ile Ser Ala Ile Asn				
		435		440	445
55	Pro His Lys Ala Ile Phe Ile Asn Lys Thr Phe Asn Leu Asp Ala Ser				
		450		455	460
60	Tyr Trp His Leu Lys Ser Val Val Phe Asp Gly Asn Val Asp Asn Gly				
		465		470	475 480
65	Asn Asn Lys Pro Ala Tyr Leu Arg Ile Ala Gly Ser Tyr Asn Ile Ile				
		485		490	495
70	Glu His Val Ile Ala Arg Asn Asn Asp Asp Thr Gly Ile Ser Ile Ser				
		500		505	510

EP 1 342 784 A1

5 Ala Lys Asp Lys Asn Arg Phe Phe Trp Pro Ala His Asn Leu Val Leu  
515 520 525

Asn Ser Asp Ser Tyr Asn Asn Leu Asp Leu Ser Gly Ile Asn Ala Asp  
530 535 540

10 Gly Phe Ala Ala Lys Leu Gly Val Gly Pro Gly Asn Ile Phe Arg Gly  
545 550 555 560

15 Cys Ile Ala His Asn Asn Ala Asp Asp Gly Trp Asp Leu Phe Asn Lys  
565 570 575

Ile Glu Asp Gly Pro Asn Ala Ser Val Thr Ile Glu Asn Ser Val Ala  
580 585 590

20 Tyr Glu Asn Gly Leu Pro Tyr Asn Lys Ala Asp Ile Leu Lys Gly Ser  
595 600 605

25 Ile Gly Asn Gly Gly Glu Gly Gln Pro Ser Lys Ser Gln Val Ile Asn  
610 615 620

30 Ser Ile Ala Ile Asn Asn Asn Met Asp Gly Phe Thr Asp Asn Phe Asn  
625 630 635 640

35 Thr Gly Ser Leu Ile Val Arg Asn Asn Ile Ala Met Asn Asn Ala Arg  
645 650 655

Tyr Asn Tyr Ile Leu Arg Thr Asn Pro Tyr Lys Phe Pro Ser Ser Ile  
660 665 670

40 Leu Phe Asp Asn Asn Tyr Ser Ile Arg Asp Asp Trp Glu Asn Lys Ile  
675 680 685

45 Lys Asp Phe Leu Gly Asp Thr Val Asn Ser Val Asn Tyr Lys Leu Leu  
690 695 700

50 Val Ser His Glu Thr Gly Pro Val Gln Lys Asp Leu Phe Phe Thr Arg  
705 710 715 720

Asp Asp Ser Gly Asn Ile Ile Tyr Pro Asp Phe Phe Leu Asn Ile Ile  
725 730 735

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EP 1 342 784 A1

Asn Lys Phe Asn Glx Thr Met Pro  
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Met Lys Thr Phe Ile Lys Thr Leu Leu Val Ala Val Thr Ile Leu Phe  
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Ser Val Phe Ala Thr Ala Lys Gln Val Lys Leu Pro Asn Asn Ile Lys  
20 25 30

20

Tyr Val Asn Thr Thr Glu Ala Phe Ser Cys Thr Glu Ile Asp Gly Met  
35 40 45

25

Asn Cys Gln Thr Lys Asn Pro Phe Asn Tyr Lys Asp Asn Ser Tyr Val  
50 55 60

Phe Val Leu Glu Arg Gly Gly Ala Trp Cys Tyr Asp Tyr Thr Val Ser  
65 70 75 80

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Val Leu Asn Leu Lys Thr Gly Lys Ala Gln Met Leu Glu Tyr Lys Asp  
85 90 95

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Asn Gln Leu Cys Ser Gly Ser Asn Lys Pro Phe Phe Glu Ile Lys Asn  
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Gly Val Pro Thr Val Gly Val Ile Asp Thr Ser Gly Lys Pro Val Val  
115 120 125

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Val Ala Leu Asp Lys Leu Lys Thr  
130 135

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Met Gln Leu Pro Val Lys Leu Leu Met Ser Leu Ile Ser Leu Val Ser  
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EP 1 342 784 A1

Val Ile Ala Arg Ala Gly Lys Tyr Lys Asn Tyr Ile Arg Asp Glu Ile  
20 25 30

5 Lys Tyr Trp Arg Tyr Thr Ser Tyr Lys Gly Gly Glu Phe Pro Glu Gly  
35 40 45

10 Phe Thr Asp Glu Lys Phe Ser Ser Ala Ile Tyr Asn Gly Arg Ile Phe  
50 55 60

15 Thr Met Lys Arg Leu His Thr Leu Met Leu Phe Leu Ala Val Leu Phe  
65 70 75 80

Thr Gly Phe Asn Val Glu Ala Ala Ser Val Lys Gln Ala Leu Ser Cys  
85 90 95

20 Asp Pro Asn Ala Arg Ala Glu Gln Pro Gly Ala Cys Pro Thr Thr Tyr  
100 105 110

25 Glu Leu Tyr Glu Gly Asp Ala Ala Tyr Lys Ala Ala Leu Asp Lys Ala  
115 120 125

Leu Lys Pro Val Gly Leu Ser Gly Met Phe Gly Lys Gly Gly Tyr Met  
130 135 140

30 Asp Gly Pro Gly Gly Asn Val Thr Pro Val Thr Ile Asn Gly Thr Val  
145 150 155 160

35 Trp Leu Gln Gly Asp Gly Cys Lys Ala Asn Thr Cys Gly Trp Asp Phe  
165 170 175

Ile Val Thr Leu Tyr Asn Pro Lys Thr His Glu Val Val Gly Tyr Arg  
180 185 190

40 Tyr Phe Gly Leu Asp Asp Pro Ala Tyr Leu Val Trp Phe Gly Glu Ile  
195 200 205

45 Gly Val His Glu Phe Ala Tyr Leu Val Lys Asn Tyr Val Ala Ala Val  
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50 Asn  
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<210> 49

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EP 1 342 784 A1

<211> 721  
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Phe Ile Pro Leu His Ala His Ala Ser Ser Thr Ser Glu Asp Glu Met  
 20 25 30

15

Ile Val Thr Gly Asn Thr Ala Ala Asp Thr Thr Asp Ser Ala Ala Gly  
 35 40 45

Ala Gly Phe Lys Thr Asn Asp Ile Asp Val Gly Pro Leu Gly Thr Lys  
 50 55 60

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Ser Trp Ile Glu Thr Pro Tyr Ser Ser Thr Thr Val Thr Lys Glu Met  
 65 70 75 80

25

Ile Glu Asn Gln Gln Ala Gln Ser Val Ser Glu Met Leu Lys Tyr Ser  
 85 90 95

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Pro Ser Thr Gln Met Gln Ala Arg Gly Gly Met Asp Val Gly Arg Pro  
 100 105 110

Gln Ser Arg Gly Met Gln Gly Ser Val Val Ala Asn Ser Arg Leu Asp  
 115 120 125

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Gly Leu Asn Ile Val Ser Thr Thr Ala Phe Pro Val Glu Met Leu Glu  
 130 135 140

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Arg Met Asp Val Leu Asn Ser Leu Thr Gly Ala Leu Tyr Gly Pro Ala  
 145 150 155 160

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Ser Pro Ala Gly Gln Phe Asn Phe Val Ala Lys Arg Pro Thr Glu Glu  
 165 170 175

Thr Leu Arg Lys Val Thr Leu Gly Tyr Gln Ser Arg Ser Ala Phe Thr  
 180 185 190

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Gly His Ala Asp Leu Gly Gly His Phe Asp Glu Asn Lys Arg Phe Gly  
 195 200 205

55

EP 1 342 784 A1

Tyr Arg Val Asn Leu Leu Asp Gln Glu Gly Glu Gly Asn Val Asp Asp  
 210 215 220  
 5 Ser Thr Leu Arg Arg Lys Leu Val Ser Val Ala Leu Asp Trp Asn Ile  
 225 230 235 240  
 10 Gln Pro Gly Thr Gln Leu Gln Leu Asp Ala Ser His Tyr Glu Phe Ile  
 245 250 255  
 Gln Lys Gly Tyr Val Gly Ser Phe Asn Tyr Gly Pro Asn Val Lys Leu  
 260 265 270  
 15 Pro Ser Ala Pro Asn Pro Lys Asp Lys Asn Leu Ala Leu Ser Thr Ala  
 275 280 285  
 20 Gly Asn Asp Leu Thr Thr Asp Thr Ile Ser Thr Arg Leu Ile His Tyr  
 290 295 300  
 Phe Asn Asp Asp Trp Ser Met Asn Ala Gly Val Gly Trp Gln Gln Ala  
 305 310 315 320  
 25 Asp Arg Ala Met Arg Ser Val Ser Ser Lys Ile Leu Asn Asn Gln Gly  
 325 330 335  
 30 Asp Ile Ser Arg Ser Met Lys Asp Ser Thr Ala Ala Gly Arg Phe Arg  
 340 345 350  
 35 Val Leu Ser Asn Thr Ala Gly Leu Asn Gly His Ile Asp Thr Gly Ser  
 355 360 365  
 40 Ile Gly His Asp Leu Ser Leu Ser Thr Thr Gly Tyr Val Trp Ser Leu  
 370 375 380  
 Tyr Ser Ala Lys Gly Thr Gly Ser Ser Tyr Ser Trp Gly Thr Thr Asn  
 385 390 395 400  
 45 Met Tyr His Pro Asp Ala Ile Asp Glu Gln Gly Asp Gly Lys Ile Arg  
 405 410 415  
 50 Thr Gly Gly Pro Arg Tyr Arg Ser Ser Val Asn Thr Gln Gln Ser Val  
 420 425 430  
 55 Thr Leu Gly Asp Thr Val Thr Phe Thr Pro Gln Trp Ser Ala Met Phe

EP 1 342 784 A1

	435	440	445
5	Tyr Leu Ser Gln Ser Trp Leu Gln Thr Lys Asn Tyr Asp Lys His Gly 450 455 460		
10	Asn Gln Thr Asn Gln Val Asp Glu Asn Gly Leu Ser Pro Asn Ala Ala 465 470 475 480		
	Leu Met Tyr Lys Ile Thr Pro Asn Thr Met Ala Tyr Val Ser Tyr Ala 485 490 495		
15	Asp Ser Leu Glu Gln Gly Gly Thr Ala Pro Thr Asp Glu Ser Val Lys 500 505 510		
20	Asn Ala Gly Gln Thr Leu Asn Pro Tyr Arg Ser Lys Gln Tyr Glu Val 515 520 525		
	Gly Leu Lys Ser Asp Ile Gly Glu Met Asn Leu Gly Ala Ala Leu Phe 530 535 540		
25	Arg Leu Glu Arg Pro Phe Ala Tyr Leu Asp Thr Asp Asn Val Tyr Lys 545 550 555 560		
30	Glu Gln Gly Asn Gln Val Asn Asn Gly Leu Glu Leu Thr Ala Ala Gly 565 570 575		
35	Asn Val Trp Gln Gly Leu Asn Ile Tyr Ser Gly Val Thr Phe Leu Asp 580 585 590		
	Pro Lys Leu Lys Asp Thr Ala Asn Ala Ser Thr Ser Asn Lys Gln Val 595 600 605		
40	Val Gly Val Pro Lys Val Gln Ala Asn Leu Leu Ala Glu Tyr Ser Leu 610 615 620		
45	Pro Ser Ile Pro Glu Trp Val Tyr Ser Ala Asn Val His Tyr Thr Gly 625 630 635 640		
50	Lys Arg Ala Ala Asn Asp Thr Asn Thr Ser Tyr Ala Ser Ser Tyr Thr 645 650 655		
55	Thr Trp Asp Leu Gly Thr Arg Tyr Thr Thr Lys Val Ser Asn Val Pro 660 665 670		



EP 1 342 784 A1

5 Thr Thr Phe Arg Val Val Val Asn Asn Val Phe Asp Lys His Tyr Trp  
675 680 685

Ala Ser Ile Phe Pro Ser Gly Thr Asp Gly Asp Asn Gly Ser Pro Ser  
690 695 700

10 Ala Phe Ile Gly Gly Gly Arg Glu Val Arg Ala Ser Val Thr Phe Asp  
705 710 715 720

15 Phe

<210> 50  
<211> 669  
20 <212> PRT  
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25 Met Lys Asn Ile Thr Leu Trp Gln Arg Leu Arg Gln Val Ser Ile Ser  
1 5 10 15

Thr Ser Leu Arg Cys Ala Phe Leu Met Gly Ala Leu Leu Thr Leu Ile  
20 25 30

30 Val Ser Ser Val Ser Leu Tyr Ser Trp His Glu Gln Ser Ser Gln Ile  
35 40 45

Arg Tyr Ser Leu Asp Lys Tyr Phe Pro Arg Ile His Ser Ala Phe Leu  
50 55 60

40 Ile Glu Gly Asn Leu Asn Leu Val Val Asp Gln Leu Asn Glu Phe Leu  
65 70 75 80

Gln Ala Pro Asn Thr Thr Val Arg Leu Gln Leu Arg Thr Gln Ile Ile  
85 90 95

45 Gln His Leu Asp Thr Ile Glu Arg Leu Ser Arg Gly Leu Ser Ser Arg  
100 105 110

50 Glu Arg Gln Gln Leu Thr Val Ile Leu Gln Asp Ser Arg Ser Leu Leu  
115 120 125

55 Ser Glu Leu Asp Arg Ala Leu Tyr Asn Met Phe Leu Leu Arg Glu Lys

# EP 1 342 784 A1

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5	Val	Ser	Glu	Leu	Ser	Ala	Arg	Ile	Asp	Trp	Leu	His	Asp	Asp	Phe	Thr	
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	Thr	Glu	Leu	Asn	Ser	Leu	Val	Gln	Asp	Phe	Thr	Trp	Gln	Gln	Gly	Thr	
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	Leu	Leu	Asp	Gln	Ile	Ala	Ser	Arg	Gln	Gly	Asp	Thr	Ala	Gln	Tyr	Leu	
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	Ala	Arg	Ile	Glu	Asn	Gln	Ile	Val	Asp	Asp	Leu	Arg	Asp	Arg	Leu	Asn	
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	Glu	Leu	Lys	Ser	Gly	Arg	Asp	Asp	Asp	Ile	Gln	Val	Glu	Thr	His	Leu	
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	Arg	Tyr	Phe	Glu	Asn	Leu	Lys	Lys	Thr	Ala	Asp	Glu	Asn	Ile	Arg	Met	
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30	Leu	Asp	Asp	Trp	Pro	Gly	Thr	Ile	Thr	Leu	Arg	Gln	Thr	Ile	Asp	Glu	
				260					265					270			
	Leu	Leu	Asp	Met	Gly	Ile	Val	Lys	Asn	Lys	Met	Pro	Asp	Thr	Met	Arg	
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	Glu	Tyr	Val	Ala	Ala	Gln	Lys	Ala	Leu	Glu	Asp	Ala	Ser	Arg	Thr	Arg	
		290					295					300					
40	Glu	Ala	Thr	Gln	Gly	Arg	Phe	Arg	Thr	Leu	Leu	Glu	Ala	Gln	Leu	Gly	
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	Ser	Thr	His	Gln	Gln	Met	Gln	Met	Phe	Asn	Gln	Arg	Met	Glu	Gln	Ile	
45					325					330					335		
	Val	His	Val	Ser	Gly	Gly	Leu	Ile	Leu	Val	Ala	Thr	Ala	Leu	Ala	Leu	
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	Leu	Leu	Ala	Trp	Val	Phe	Asn	His	Tyr	Phe	Ile	Arg	Ser	Arg	Leu	Val	
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EP 1 342 784 A1

5 Lys Arg Phe Thr Leu Leu Asn Gln Ala Val Val Gln Ile Gly Leu Gly  
370 375 380

Gly Thr Glu Thr Thr Ile Pro Val Tyr Gly Asn Asp Glu Leu Gly Arg  
385 390 395 400

10 Ile Ala Gly Leu Leu Arg His Thr Leu Gly Gln Leu Asn Val Gln Lys  
405 410 415

15 Gln Gln Leu Glu Gln Glu Ile Thr Asp Arg Lys Val Ile Glu Ala Asp  
420 425 430

20 Leu Arg Ala Thr Gln Asp Glu Leu Ile Gln Thr Ala Lys Leu Ala Val  
435 440 445

25 Val Gly Gln Thr Met Thr Thr Leu Ala His Glu Ile Asn Gln Pro Leu  
450 455 460

Asn Ala Leu Ser Met Tyr Leu Phe Thr Ala Arg Arg Ala Ile Glu Gln  
465 470 475 480

30 Thr Gln Lys Glu Gln Ala Ser Met Met Leu Gly Lys Ala Glu Gly Val  
485 490 495

Ile Ser Arg Ile Asp Ala Ile Ile Arg Ser Leu Arg Gln Phe Thr Arg  
500 505 510

35 Arg Ala Glu Leu Glu Thr Ser Leu His Ala Val Asp Leu Ala Gln Met  
515 520 525

40 Phe Ser Ala Ala Trp Glu Leu Leu Ala Met Arg His Arg Ser Leu Gln  
530 535 540

45 Ala Thr Leu Val Leu Pro Gln Gly Thr Ala Thr Val Ser Gly Asp Glu  
545 550 555 560

Val Arg Thr Gln Gln Val Leu Val Asn Val Leu Ala Asn Ala Leu Asp  
565 570 575

50 Val Cys Gly Gln Gly Ala Val Ile Thr Val Asn Trp Gln Met Gln Gly  
580 585 590

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# EP 1 342 784 A1

Lys Thr Leu Asn Val Phe Ile Gly Asp Asn Gly Pro Gly Trp Pro Glu  
 595 600 605  
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 Ala Leu Leu Pro Ser Leu Leu Lys Pro Phe Thr Thr Ser Lys Glu Val  
 610 615 620  
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 Gly Leu Gly Ile Gly Leu Ser Ile Cys Val Ser Leu Met Glu Gln Met  
 625 630 635 640  
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 Lys Gly Glu Leu Arg Leu Ala Ser Thr Met Thr Arg Asn Ala Cys Val  
 645 650 655  
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 Val Leu Gln Phe Arg Leu Thr Asp Val Glu Asp Ala Lys  
 660 665  
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 <210> 51  
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 <212> PRT  
 <213> Escherichia coli  
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 Met Asn Val Ile Lys Leu Ala Ile Gly Ser Gly Ile Leu Leu Leu Ser  
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 Cys Gly Ala Tyr Ser Gln Ser Ile Ser Glu Lys Thr Asn Ser Asp Lys  
 20 25 30  
 40  
 Lys Gly Ala Ala Glu Phe Ser Pro Leu Ser Val Ser Val Gly Lys Thr  
 35 40 45  
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 Thr Ser Glu Gln Glu Ala Leu Glu Lys Thr Gly Ala Thr Ser Ser Arg  
 50 55 60  
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 Thr Thr Asp Lys Asn Leu Gln Ser Leu Asp Ala Thr Val Arg Ser Met  
 65 70 75 80  
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 Pro Gly Thr Tyr Thr Gln Ile Asp Pro Gly Gln Gly Ala Ile Ser Val  
 85 90 95  
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 Asn Ile Arg Gly Met Ser Gly Phe Gly Arg Val Asn Thr Met Val Asp  
 100 105 110  
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 Gly Ile Thr Gln Ser Phe Tyr Gly Thr Ser Thr Ser Gly Thr Thr Thr  
 115 120 125  
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EP 1 342 784 A1

5 His Gly Ser Thr Asn Asn Met Ala Gly Val Leu Ile Asp Pro Asn Leu  
130 135 140

10 Leu Val Ala Val Asp Val Thr Arg Gly Asp Ser Ser Gly Ser Glu Gly  
145 150 155 160

15 Ile Asn Ala Leu Ala Gly Ser Ala Asn Met Arg Thr Ile Gly Val Asp  
165 170 175

20 Asp Val Ile Phe Asn Gly Asn Thr Tyr Gly Leu Arg Ser Arg Phe Ser  
180 185 190

25 Val Gly Ser Asn Gly Leu Gly Arg Ser Gly Met Ile Ala Leu Gly Gly  
195 200 205

30 Lys Ser Asp Ala Phe Thr Asp Thr Gly Ser Ile Gly Val Met Ala Ala  
210 215 220

35 Val Ser Gly Ser Ser Val Tyr Ser Asn Phe Ser Asn Gly Ser Gly Ile  
225 230 235 240

40 Asn Ser Lys Glu Phe Gly Tyr Asp Lys Tyr Met Lys Gln Asn Pro Lys  
245 250 255

45 Ser Gln Leu Tyr Lys Met Asp Ile Arg Pro Asp Glu Phe Asn Ser Phe  
260 265 270

50 Glu Leu Ser Ala Arg Thr Tyr Glu Asn Lys Phe Thr Arg Arg Asp Ile  
275 280 285

55 Thr Ser Asp Asp Tyr Tyr Ile Lys Tyr His Tyr Thr Pro Phe Ser Glu  
290 295 300

60 Leu Ile Asp Phe Asn Val Thr Ala Ser Thr Ser Arg Gly Asn Gln Lys  
305 310 315 320

65 Tyr Arg Asp Gly Ser Leu Tyr Thr Phe Tyr Lys Thr Ser Ala Gln Asn  
325 330 335

70 Arg Ser Asp Ala Leu Asp Ile Asn Asn Thr Ser Arg Phe Thr Val Ala  
340 345 350

EP 1 342 784 A1

Asp Asn Asp Leu Glu Phe Met Leu Gly Ser Lys Leu Met Arg Thr Arg  
 355 360 365  
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 Tyr Asp Arg Thr Ile His Ser Ala Ala Gly Asp Pro Lys Ala Asn Gln  
 370 375 380  
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 Glu Ser Ile Glu Asn Asn Pro Phe Ala Pro Ser Gly Gln Gln Asp Ile  
 385 390 395 400  
 Ser Ala Leu Tyr Thr Gly Leu Lys Val Thr Arg Gly Ile Trp Glu Ala  
 405 410 415  
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 Asp Phe Asn Leu Asn Tyr Thr Arg Asn Arg Ile Thr Gly Tyr Lys Pro  
 420 425 430  
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 Ala Cys Asp Ser Arg Val Ile Cys Val Pro Gln Gly Ser Tyr Asp Ile  
 435 440 445  
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 Asp Asp Lys Glu Gly Gly Phe Asn Pro Ser Val Gln Leu Ser Ala Gln  
 450 455 460  
 Val Thr Pro Trp Leu Gln Pro Phe Ile Gly Tyr Ser Lys Ser Met Arg  
 465 470 475 480  
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 Ala Pro Asn Ile Gln Glu Met Phe Phe Ser Asn Ser Gly Gly Ala Ser  
 485 490 495  
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 Met Asn Pro Phe Leu Lys Pro Glu Arg Ala Glu Thr Trp Gln Ala Gly  
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 Phe Asn Ile Asp Thr Arg Asp Leu Leu Val Glu Gln Asp Ala Leu Arg  
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 Phe Lys Ala Leu Ala Tyr Arg Ser Arg Ile Gln Asn Tyr Ile Tyr Ser  
 530 535 540  
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 Glu Ser Tyr Leu Val Cys Ser Gly Gly Arg Lys Cys Ser Leu Pro Glu  
 545 550 555 560  
 Val Ile Gly Asn Gly Trp Glu Gly Ile Ser Asp Glu Tyr Ser Asp Asn  
 565 570 575  
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EP 1 342 784 A1

Met Tyr Ile Tyr Val Asn Ser Ala Ser Asp Val Ile Ala Lys Gly Phe  
580 585 590

5 Glu Leu Glu Met Asp Tyr Asp Ala Gly Phe Ala Phe Gly Arg Leu Ser  
595 600 605

10 Phe Ser Gln Gln Gln Thr Asp Gln Pro Thr Ser Ile Ala Ser Thr His  
610 615 620

15 Phe Gly Ala Gly Asp Ile Thr Glu Leu Pro Arg Lys Tyr Met Thr Leu  
625 630 635 640

Asp Thr Gly Val Arg Phe Phe Asp Asn Ala Leu Thr Leu Gly Thr Ile  
645 650 655

20 Ile Lys Tyr Thr Gly Lys Ala Arg Arg Leu Ser Pro Asp Phe Glu Gln  
660 665 670

25 Asp Glu His Thr Gly Ala Ile Ile Lys Gln Asp Leu Pro Gln Ile Pro  
675 680 685

30 Thr Ile Ile Asp Leu Tyr Gly Thr Tyr Glu Tyr Asn Arg Asn Leu Thr  
690 695 700

Leu Lys Leu Ser Val Gln Asn Leu Met Asn Arg Asp Tyr Ser Glu Ala  
705 710 715 720

35 Leu Asn Lys Leu Asn Met Met Pro Gly Leu Gly Asp Glu Thr His Pro  
725 730 735

40 Ala Asn Ser Ala Arg Gly Arg Thr Trp Ile Phe Gly Gly Asp Ile Arg  
740 745 750

Phe

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<210> 52  
<211> 133  
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<213> Escherichia coli  
50 <400> 52

Met Ser Ser Lys Thr Lys Cys Trp Leu Trp Met Leu Leu Val Ile Leu  
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# EP 1 342 784 A1

Ser Glu Thr Ser Ala Thr Ser Thr Leu Lys Met Phe Asp Asn Ser Glu  
 20 25 30  
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 Gly Met Thr Lys Thr Leu Leu Leu Ala Leu Ile Val Val Leu Tyr Cys  
 35 40 45  
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 Ile Cys Tyr Tyr Ser Leu Ser Arg Ala Val Lys Asp Ile Pro Val Gly  
 50 55 60  
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 Leu Ala Tyr Ala Thr Trp Ser Gly Thr Gly Ile Leu Met Val Ser Thr  
 65 70 75 80  
 Leu Gly Ile Leu Phe Tyr Gly Gln His Pro Asp Thr Ala Ala Ile Ile  
 85 90 95  
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 Gly Met Val Ile Ile Ala Ser Gly Ile Ile Ile Met Asn Leu Phe Ser  
 100 105 110  
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 Lys Met Gly Ser Glu Glu Ala Glu Glu Thr Pro Val Thr Asn Leu Asp  
 115 120 125  
 Lys Lys Ile Ala Asn  
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 <212> PRT  
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 Met Tyr Ile Lys Lys His Trp Ile Ala Leu Ser Ile Leu Leu Ile Pro  
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 Cys Ile Gly Asn Ala Gln Glu Ile Lys Ile Asp Glu Ser Trp Leu His  
 20 25 30  
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 Gln Ser Leu Asn Val Ile Gly Arg Thr Asp Ser Arg Phe Gly Pro Arg  
 35 40 45  
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 Leu Thr Asn Asp Leu Tyr Pro Glu Tyr Thr Val Ala Gly Arg Lys Asp  
 50 55 60  
 Trp Phe Asp Phe Tyr Gly Tyr Val Asp Leu Pro Lys Phe Phe Gly Val  
 65 70 75 80  
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EP 1 342 784 A1

5 Gly Ser His Tyr Asp Val Gly Ile Trp Asp Glu Gly Ser Pro Leu Phe  
85 90 95

Thr Glu Ile Glu Pro Arg Phe Ser Ile Asp Lys Leu Thr Gly Leu Asn  
100 105 110

10 Leu Ala Phe Gly Pro Phe Lys Glu Trp Phe Ile Ala Asn Asn Tyr Val  
115 120 125

15 Tyr Asp Met Gly Asp Asn Gln Ser Ser Arg Gln Ser Thr Trp Tyr Met  
130 135 140

Gly Leu Gly Thr Asp Ile Asp Thr Gly Leu Pro Ile Lys Leu Ser Ala  
145 150 155 160

20 Asn Ile Tyr Ala Lys Tyr Gln Trp Gln Asn Tyr Gly Ala Ala Asn Glu  
165 170 175

25 Asn Glu Trp Asp Gly Tyr Arg Phe Lys Ile Lys Tyr Ser Ile Pro Leu  
180 185 190

30 Thr Asn Leu Phe Gly Gly Arg Leu Val Tyr Asn Ser Phe Thr Asn Phe  
195 200 205

Asp Phe Gly Ser Asp Leu Ala Asp Lys Ser His Asn Asn Lys Arg Thr  
210 215 220

35 Ser Asn Ala Ile Ala Ser Ser His Ile Leu Ser Leu Leu Tyr Glu His  
225 230 235 240

40 Trp Lys Phe Ala Phe Thr Leu Arg Tyr Phe His Asn Gly Gly Gln Trp  
245 250 255

45 Asn Ala Gly Glu Lys Val Asn Phe Gly Asp Gly Pro Phe Glu Leu Lys  
260 265 270

Asn Thr Gly Trp Gly Thr Tyr Thr Thr Ile Gly Tyr Gln Phe  
275 280 285

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<210> 54  
<211> 172  
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EP 1 342 784 A1

<213> Escherichia coli  
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Ile Val Ala Ser Gly Phe Ser Phe Trp Arg Leu Ser Pro Ala Glu Asn  
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10 Thr Gly Ile Met Ser Cys Ser Thr Lys Gly Ile Met Arg Phe Glu Asn  
35 40 45

15 Met Glu Lys Glu Asn Val Asn Gly Asn Ile His Phe Asn Phe Gly Ser  
50 55 60

20 Gln Gly Lys Gly Ser Met Val Leu Glu Gly Tyr Thr Asp Ser Ala Ala  
65 70 75 80

Gly Trp Leu Tyr Leu Gln Arg Tyr Val Lys Phe Thr Tyr Thr Ser Lys  
85 90 95

25 Arg Val Ser Ala Thr Glu Arg His Tyr Arg Ile Ser Gln Trp Glu Ser  
100 105 110

30 Ser Ala Ser Ser Ile Asp Glu Ser Pro Asp Val Ile Phe Asp Tyr Phe  
115 120 125

35 Met Arg Glu Met Ser Asp Ser His Asp Gly Leu Phe Leu Asn Ala Gln  
130 135 140

Lys Leu Asn Asp Lys Ala Ile Leu Leu Ser Ser Ile Asn Ser Pro Leu  
145 150 155 160

40 Trp Ile Cys Thr Leu Lys Ser Gly Ser Lys Leu Asp  
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45 <210> 55  
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<213> Escherichia coli  
<400> 55

50 Met Lys Ile Lys Val Ile Ala Leu Ala Thr Phe Val Ser Ala Val Phe  
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EP 1 342 784 A1

Ala Gly Ser Ala Met Ala Tyr Asp Gly Thr Ile Thr Phe Thr Gly Lys  
20 25 30

5 Val Val Ala Gln Thr Cys Thr Val Asn Thr Ser Asp Lys Asp Leu Ala  
35 40 45

10 Val Thr Leu Pro Thr Val Ala Thr Ser Ser Leu Lys Asp Asn Ala Ala  
50 55 60

15 Thr Ser Gly Leu Thr Pro Phe Ala Ile Arg Leu Thr Gly Cys Ala Thr  
65 70 75 80

Gly Met Asn Ser Ala Gln Asn Val Lys Ala Tyr Phe Glu Pro Ser Ser  
85 90 95

20 Asn Ile Asp Leu Ala Thr His Asn Leu Lys Asn Thr Ala Thr Pro Thr  
100 105 110

25 Lys Ala Asp Asn Val Gln Ile Gln Leu Leu Asn Ser Asn Gly Thr Ser  
115 120 125

30 Thr Ile Leu Leu Gly Glu Ala Asp Asn Gly Gln Asp Val Gln Ser Glu  
130 135 140

Thr Ile Gly Ser Asp Gly Ser Ala Thr Leu Arg Tyr Met Ala Gln Tyr  
145 150 155 160

35 Tyr Ala Thr Gly Gln Ser Thr Ala Gly Asp Val Lys Ala Thr Val His  
165 170 175

40 Tyr Thr Ile Ala Tyr Glu  
180

45 <210> 56  
<211> 359  
<212> PRT  
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<400> 56

Met Lys Arg Ile Phe Phe Ile Pro Leu Phe Leu Ile Leu Leu Pro Lys  
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50 Leu Ala Val Ala Gly Pro Asp Asp Tyr Val Pro Ser Gln Ile Ala Val  
20 25 30

55

EP 1 342 784 A1

5 Asn Thr Ser Thr Leu Pro Gly Val Val Ile Gly Pro Ala Asp Ala His  
 35 40 45  
 10 Thr Tyr Pro Arg Val Ile Gly Glu Leu Ala Gly Thr Ser Asn Gln Tyr  
 50 55 60  
 15 Val Phe Asn Gly Gly Ala Ile Ala Leu Met Arg Gly Lys Phe Thr Pro  
 65 70 75 80  
 20 Ala Leu Pro Lys Ile Gly Ser Ile Thr Val Tyr Phe Pro Ser Arg Lys  
 85 90 95  
 25 Gln Arg Asp Ser Ser Asp Phe Asp Ile Tyr Asp Ile Gly Val Ser Gly  
 100 105 110  
 30 Leu Gly Ile Ile Ile Gly Met Ala Gly Tyr Trp Pro Ala Thr Pro Leu  
 115 120 125  
 35 Val Pro Ile Asn Ser Ser Gly Ile Tyr Ile Asp Pro Val Gly Ala Asn  
 130 135 140  
 40 Thr Asn Pro Asn Thr Tyr Asn Gly Ala Thr Ala Ser Phe Gly Ala Arg  
 145 150 155 160  
 45 Leu Phe Val Ala Phe Val Ala Thr Gly Arg Leu Pro Asn Gly Tyr Ile  
 165 170 175  
 50 Thr Ile Pro Thr Arg Gln Leu Gly Thr Ile Leu Leu Glu Ala Lys Arg  
 180 185 190  
 55 Thr Ser Leu Asn Asn Lys Gly Leu Thr Ala Pro Val Met Leu Asn Gly  
 195 200 205  
 60 Gly Arg Ile Gln Val Gln Ser Gln Thr Cys Thr Met Gly Gln Lys Asn  
 210 215 220  
 65 Tyr Val Val Pro Leu Asn Thr Val Tyr Gln Ser Gln Phe Thr Ser Leu  
 225 230 235 240  
 70 Tyr Lys Glu Ile Gln Gly Gly Lys Ile Asp Ile His Leu Gln Cys Pro  
 245 250 255

EP 1 342 784 A1

Asp Gly Ile Asp Val Tyr Ala Thr Leu Thr Asp Ala Ser Gln Pro Val  
260 265 270

5 Asn Arg Thr Asp Ile Leu Thr Leu Ser Ser Glu Ser Thr Ala Lys Gly  
275 280 285

10 Phe Gly Ile Arg Leu Tyr Lys Asp Ser Asp Val Thr Ala Ile Ser Tyr  
290 295 300

Gly Glu Asp Ser Pro Val Lys Gly Asn Gly Ser Gln Trp His Phe Ser  
305 310 315 320

15 Asp Tyr Arg Gly Glu Val Asn Pro His Ile Asn Leu Arg Ala Asn Tyr  
325 330 335

20 Ile Lys Ile Ala Asp Ala Thr Thr Pro Gly Ser Val Lys Ala Ile Ala  
340 345 350

Thr Ile Thr Phe Ser Tyr Gln  
355

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<210> 57  
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<212> PRT  
30 <213> Escherichia coli  
<400> 57

Met Asn Ala Asn Asn Leu Ser Cys Leu Ile Tyr Cys Arg Cys Ser Leu  
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35 Leu Leu Phe Ala Ala Leu Gly Leu Thr Val Thr Asn His Ser Phe Ala  
20 25 30

40 Ala Glu Glu Ala Glu Phe Asp Ser Glu Phe Leu His Leu Asp Lys Gly  
35 40 45

45 Ile Asn Ala Ile Asp Ile Arg Arg Phe Ser His Gly Asn Pro Val Pro  
50 55 60

Glu Gly Arg Tyr Tyr Ser Asp Ile Tyr Val Asn Asn Val Trp Lys Gly  
65 70 75 80

50 Lys Ala Asp Leu Gln Tyr Leu Arg Thr Ala Asn Thr Gly Ala Pro Thr  
85 90 95

55

# EP 1 342 784 A1

Leu Cys Leu Thr Pro Glu Leu Leu Ser Leu Ile Asp Leu Val Lys Asp  
 100 105 110  
 5  
 Thr Met Ser Gly Asn Thr Ser Cys Phe Pro Ala Ser Thr Gly Leu Ser  
 115 120 125  
 10  
 Ser Ala Arg Ile Asn Phe Asp Leu Ser Thr Leu Arg Leu Asn Ile Glu  
 130 135 140  
 15  
 Ile Pro Gln Ala Leu Leu Asn Thr Arg Pro Arg Gly Tyr Ile Ser Pro  
 145 150 155 160  
 Ala Gln Trp Gln Ser Gly Val Pro Ala Ala Phe Ile Asn Tyr Asp Ala  
 165 170 175  
 20  
 Asn Tyr Tyr Gln Tyr Ser Ser Ser Gly Thr Ser Asn Glu Gln Thr Tyr  
 180 185 190  
 25  
 Leu Gly Leu Lys Ala Gly Phe Asn Leu Trp Gly Trp Ala Leu Arg His  
 195 200 205  
 30  
 Arg Gly Ser Glu Ser Trp Asn Asn Ser Tyr Pro Ala Gly Tyr Gln Asn  
 210 215 220  
 Ile Glu Thr Ser Ile Met His Asp Leu Ala Pro Leu Arg Ala Gln Phe  
 225 230 235 240  
 35  
 Thr Leu Gly Asp Phe Tyr Thr Asn Gly Glu Leu Met Asp Ser Leu Ser  
 245 250 255  
 40  
 Leu Arg Gly Val Arg Leu Ala Ser Asp Glu Arg Met Leu Pro Gly Ser  
 260 265 270  
 45  
 Leu Arg Gly Tyr Ala Pro Ala Val Arg Gly Ile Ala Asn Ser Asn Ala  
 275 280 285  
 Lys Val Thr Ile Tyr Gln Asn Ala His Ile Leu Tyr Glu Thr Thr Val  
 290 295 300  
 50  
 Pro Ala Gly Pro Phe Val Ile Asn Asp Leu Tyr Pro Ser Gly Tyr Ala  
 305 310 315 320  
 55

EP 1 342 784 A1

Gly Asp Leu Leu Val Lys Ile Thr Glu Ser Asn Gly Gln Thr Arg Met  
325 330 335

5 Phe Thr Val Pro Phe Ala Ala Val Ala Gln Leu Ile Arg Pro Gly Phe  
340 345 350

10 Ser Arg Trp Gln Met Ser Val Gly Lys Tyr Arg Tyr Ala Asn Lys Thr  
355 360 365

15 Tyr Asn Asp Leu Ile Ala Gln Gly Thr Tyr Gln Tyr Gly Leu Thr Asn  
370 375 380

Asp Ile Thr Leu Asn Ser Gly Leu Thr Thr Ala Ser Gly Tyr Thr Ala  
385 390 395 400

20 Gly Leu Ala Gly Leu Ala Phe Asn Thr Pro Leu Gly Ala Ile Ala Ser  
405 410 415

25 Asp Ile Thr Leu Ser Arg Thr Ala Phe Arg Tyr Ser Gly Val Thr Arg  
420 425 430

Lys Gly Tyr Ser Leu His Ser Ser Tyr Ser Ile Asn Ile Pro Ala Ser  
435 440 445

30 Asn Thr Asn Ile Thr Leu Ala Ala Tyr Arg Tyr Ser Ser Lys Asp Phe  
450 455 460

35 Tyr His Leu Lys Asp Ala Leu Ser Ala Asn His Asn Ala Phe Ile Asp  
465 470 475 480

40 Asp Val Ser Val Lys Ser Thr Ala Phe Tyr Arg Pro Arg Asn Gln Phe  
485 490 495

Gln Ile Ser Ile Asn Gln Glu Leu Gly Glu Lys Trp Gly Gly Met Tyr  
500 505 510

45 Leu Thr Gly Thr Thr Tyr Asn Tyr Trp Gly His Lys Gly Ser Arg Asn  
515 520 525

50 Glu Tyr Gln Ile Gly Tyr Ser Asn Phe Trp Lys Gln Leu Gly Tyr Gln  
530 535 540

55 Ile Gly Leu Ser Gln Ser Arg Asp Asn Glu Gln Gln Arg Arg Asp Asp

EP 1 342 784 A1

	545		550		555		560
5	Arg Phe Tyr Ile Asn Phe Thr Leu Pro Leu Gly Gly Ser Val Gln Ser	565		570		575	
10	Pro Val Phe Ser Thr Val Leu Asn Tyr Ser Lys Glu Glu Lys Asn Ser	580		585		590	
15	Ile Gln Thr Ser Ile Ser Gly Thr Gly Gly Glu Asp Asn Gln Phe Ser	595		600		605	
20	Tyr Gly Ile Ser Gly Asn Ser Gln Glu Asn Gly Pro Ser Gly Tyr Ala	610		615		620	
25	Met Asn Gly Gly Tyr Arg Ser Pro Tyr Val Asn Ile Thr Thr Thr Val	625		630		635	640
30	Gly His Asp Thr Gln Asn Asn Asn Gln Arg Ser Phe Gly Ala Ser Gly	645		650		655	
35	Ala Val Val Ala His Pro Tyr Gly Val Thr Leu Ser Asn Asp Leu Ser	660		665		670	
40	Asp Thr Phe Ala Ile Ile His Ala Glu Gly Ala Gln Gly Ala Val Ile	675		680		685	
45	Asn Asn Ala Ser Gly Ser Arg Leu Asp Phe Trp Gly Asn Gly Val Val	690		695		700	
50	Pro Tyr Val Thr Pro Tyr Glu Lys Asn Gln Ile Ser Ile Asp Pro Ser	705		710		715	720
55	Asn Leu Asp Leu Asn Val Glu Leu Ser Ala Thr Glu Gln Glu Ile Ile	725		730		735	
	Pro Arg Ala Asn Ser Ala Thr Leu Val Lys Phe Asp Thr Lys Thr Gly	740		745		750	
	Arg Ser Leu Leu Phe Asp Ile Arg Met Ser Thr Gly Asn Pro Pro Pro	755		760		765	
	Met Ala Ser Glu Val Leu Asp Glu His Gly Gln Leu Ala Gly Tyr Val	770		775		780	



EP 1 342 784 A1

5 Ala Gln Ala Gly Lys Val Phe Thr Arg Gly Leu Pro Glu Lys Gly His  
785 790 795 800

Leu Ser Val Val Trp Gly Pro Asp Asn Lys Asp Arg Cys Ser Phe Val  
805 810 815

10 Tyr His Val Ala His Asn Lys Asp Asp Met Gln Ser Gln Leu Val Pro  
820 825 830

15 Val Leu Cys Ile Gln His Pro Asn Gln Glu Lys Thr  
835 840

20 <210> 58  
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<400> 58

25 Met Val Lys Cys His Thr Leu Ile Asn Arg Arg Asn Lys Cys Leu Leu  
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Ile Val Phe Ile Val Leu Ile Gly Trp Ile Ile Phe Arg Pro Lys Ala  
20 25 30

30 Tyr Thr Tyr Ser Leu Asn Asp Lys Glu Lys Glu Met Leu Ile Met Leu  
35 40 45

35 Ser Gln His Pro Glu Thr Arg Tyr Phe Gly Phe Tyr Ser Ile Glu Leu  
50 55 60

40 Pro Ala Asp Tyr Lys Pro Thr Gly Met Val Met Phe Ile Gln Gly Ser  
65 70 75 80

Ala Met Ile Pro Val Glu Thr Lys Leu Gln Tyr Tyr Pro Pro Phe Leu  
85 90 95

45 Gln Tyr Met Thr Arg Tyr Glu Ala Glu Leu Lys Asn Thr Ser Ala Leu  
100 105 110

50 Asp Pro Leu Asp Thr Pro Tyr Leu Lys Gln Val His Pro Leu Ser Pro  
115 120 125

55 Pro Met Asn Gly Val Ile Phe Glu Arg Met Lys Ala Lys Tyr Thr Pro

EP 1 342 784 A1

130 135 140

5 Asp Phe Ala Arg Val Leu Asp Ala Trp Lys Trp Glu Asn Gly Val Thr  
145 150 155 160

phe Ser Val Lys Ile Glu Ala Lys Asp Gly Arg Ala Thr Arg Tyr Asp  
165 170 175

10 Gly Ile Ser Lys Ile Ala Glu Tyr Ser Tyr Gly Tyr Asn Ile Pro Glu  
180 185 190

15 Lys Lys Val Gln Leu Leu Thr Ile Leu Ser Gly Leu Gln Pro Arg Ala  
195 200 205

20 Asp Asn Gln Pro Pro Ser Glu Asn Lys Leu Ala Ile Gln Tyr Ala Gln  
210 215 220

25 Val Asp Ala Ser Leu Leu Gly Glu Tyr Glu Leu Ser Val Asp Tyr Lys  
225 230 235 240

Asn Ser Asn Asn Ile Lys Ile Ser Leu Gln Thr Asp Asn Asn Ser Tyr  
245 250 255

30 Ile Asp Ser Leu Leu Asp Ile Arg Tyr Pro Ser Asn Gly Asn Arg Ala  
260 265 270

35 Trp Tyr Asn Ser Ile  
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<210> 59  
<211> 366  
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40 Met Leu Pro Glu Pro Val Tyr Arg Arg Trp Ile Ile Leu Leu Ile Ser  
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45 Met Leu Thr Val Gly Thr Leu Phe Ile Leu Ser Val Trp Asn Ser Ala  
20 25 30

50 Thr Tyr Trp Asp Ile Phe Ile Tyr Gly Val Leu Pro Met Leu Phe Leu  
35 40 45

55

EP 1 342 784 A1

Trp Leu Cys Leu Phe Gly Ile Ala Leu Asn Lys Tyr Glu Gln Ser Val  
50 55 60

5 Ala Ala Cys Ile Ser Trp Glu Ser Glu Arg Gln Gln Val Lys Gln Leu  
65 70 75 80

10 Trp Gln His Trp Ser Gln Lys Gln Leu Ala Ile Val Gly Asn Val Leu  
85 90 95

Phe Thr Pro Glu Glu Lys Gly Met Ser Val Leu Leu Gly Pro Gln Glu  
100 105 110

15 Glu Ile Pro Ala Tyr Pro Lys Lys Ala Arg Pro Leu Phe Ser Ala Ser  
115 120 125

20 Arg Tyr Ser Leu Ser Ser Ile Phe His Asp Ile His Gln Gln Leu Thr  
130 135 140

25 Gln Gln Phe Pro Asp Tyr Arg His Tyr Leu His Thr Ile Tyr Val Leu  
145 150 155 160

Gln Pro Glu Lys Trp Arg Gly Glu Thr Val Arg Gln Ala Ile Phe His  
165 170 175

30 Gln Trp Asp Leu Val Pro Glu Arg Thr Asn Thr Leu Asn Gln Ile Gln  
180 185 190

35 Ser Leu Tyr Asp Glu Arg Phe Asp Gly Leu Ile Leu Val Val Cys Leu  
195 200 205

40 Gln Asn Trp Pro Glu Asn Lys Pro Glu Asp Thr Ser Glu Leu Val Ser  
210 215 220

45 Ala Gln Leu Ile Ser Ser Ser Ser Phe Val Arg Gln His Gln Ile Pro  
225 230 235 240

Val Ile Ala Gly Leu Gly Arg Val Met Pro Leu Glu Pro Glu Glu Leu  
245 250 255

50 Glu His Asn Leu Asp Val Leu Phe Glu Tyr Asn Gln Leu Asp Asn Lys  
260 265 270

Gln Leu Gln His Val Trp Val Ser Gly Leu Asp Glu Gly Thr Ile Glu  
55

# EP 1 342 784 A1

	275	280	285
5	Asn Leu Met Gln Tyr Ala Glu Gln His Gln Trp Ser Leu Pro Lys Lys 290 295 300		
10	Arg Pro Leu His Met Ile Asp His Ser Phe Gly Pro Thr Gly Glu Phe 305 310 315 320		
15	Ile Phe Pro Val Ser Leu Ala Met Leu Ser Glu Ala Ala Lys Glu Thr 325 330 335		
20	Glu Gln Asn His Leu Ile Ile Tyr Gln Ser Ala Gln Tyr Ala Gln Lys 340 345 350		
25	Lys Ser Leu Cys Leu Ile Thr Arg Lys Leu Tyr Leu Arg Thr 355 360 365		
30	<210> 60 <211> 260 <212> PRT <213> Escherichia coli <400> 60		
35	Met Leu Asn Arg Lys Leu Asn Ile Arg Leu Arg His Ser Leu Asn Ser 1 5 10 15		
40	His Cys Ile Pro Ser Ile Ile Ile Asn Asn Thr Val Arg Ser Phe Gln 20 25 30		
45	Arg Ser Val Met Asn Thr Arg Ala Leu Phe Pro Leu Leu Phe Thr Val 35 40 45		
50	Ala Ser Phe Ser Ala Ser Ala Gly Asn Trp Ala Val Lys Asn Gly Trp 50 55 60		
55	Cys Gln Thr Met Thr Glu Asp Gly Gln Ala Leu Val Met Leu Lys Asn 65 70 75 80		
	Gly Thr Ile Gly Ile Thr Gly Leu Met Gln Gly Cys Pro Asn Gly Val 85 90 95		
	Gln Thr Leu Leu Gly Ser Arg Ile Ser Ile Asn Gly Asn Leu Ile Pro 100 105 110		

EP 1 342 784 A1

Thr Ser Gln Met Cys Asn Gln Gln Thr Gly Phe Arg Ala Val Glu Val  
115 120 125

5 Glu Ile Gly Gln Ala Pro Glu Met Val Lys Lys Ala Val His Ser Ile  
130 135 140

10 Ala Glu Arg Asp Val Ser Val Leu Gln Ala Phe Gly Val Arg Met Glu  
145 150 155 160

Phe Thr Arg Gly Asp Met Leu Lys Val Cys Pro Lys Phe Val Thr Ser  
165 170 175

15 Leu Ala Gly Phe Ser Pro Lys Gln Thr Thr Thr Ile Asn Lys Asp Ser  
180 185 190

20 Val Leu Gln Ala Ala Arg Gln Ala Tyr Ala Arg Glu Tyr Asp Glu Glu  
195 200 205

25 Thr Thr Glu Thr Ala Asp Phe Gly Ser Tyr Glu Val Lys Gly Asn Lys  
210 215 220

Val Glu Phe Glu Val Phe Asn Pro Glu Asp Arg Ala Tyr Asp Lys Val  
225 230 235 240

30 Thr Val Thr Val Gly Ala Asp Gly Asn Ala Thr Gly Ala Ser Val Glu  
245 250 255

35 Phe Ile Gly Lys  
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45 Val Val Ile Ile Asn Ser Thr Ile Leu Ser Gly Ala Gly Ala Ile Pro  
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Ser Leu Thr Ser Leu Leu Pro Asp Ile Arg Lys Met Leu Leu Val Thr  
20 25 30

50 Asp Arg Asn Ile Ala Gln Leu Asp Gly Val Gln Gln Ile Arg Ala Leu  
35 40 45

55

EP 1 342 784 A1

5 Leu Glu Lys His Cys Pro Gln Val Asn Val Ile Asp Asn Val Pro Ala  
 50 55 60  
 10 Glu Pro Thr His His Asp Val Arg Gln Leu Met Asp Ala Pro Gly Asp  
 65 70 75 80  
 15 Val Ala Lys Leu Leu Ser Val Leu Cys His Pro Gln Ser Pro Gly Leu  
 100 105 110  
 20 Asp Ala Leu Leu Ala Gly Glu Lys Pro Thr Gln Arg Val Gln Ser Trp  
 115 120 125  
 25 Leu Ile Pro Thr Thr Ala Gly Thr Gly Ser Glu Ala Thr Pro Asn Ala  
 130 135 140  
 30 Ile Leu Ala Ile Pro Glu Gln Ser Thr Lys Val Gly Ile Ile Ser Gln  
 145 150 155 160  
 35 Val Leu Leu Pro Asp Tyr Val Ala Leu Phe Pro Glu Leu Thr Thr Ser  
 165 170 175  
 40 Met Pro Ala His Ile Ala Ala Ser Thr Gly Ile Asp Ala Leu Cys His  
 180 185 190  
 45 Leu Leu Glu Cys Phe Thr Ala Thr Val Ala Asn Pro Val Ser Asp Asn  
 195 200 205  
 50 Ala Ala Leu Thr Gly Leu Ser Lys Leu Phe Arg His Ile Gln Pro Ala  
 210 215 220  
 55 Val Asn Asp Pro Gln Asp Leu Arg Ala Lys Leu Glu Met Leu Trp Ala  
 225 230 235 240  
 Ser Tyr Tyr Gly Gly Val Ala Ile Thr His Ala Gly Thr His Leu Val  
 245 250 255  
 His Ala Leu Ser Tyr Pro Leu Gly Gly Lys Tyr His Leu Pro His Gly  
 260 265 270

EP 1 342 784 A1:

Val Ala Asn Ala Ile Leu Leu Ala Pro Cys Met Ala Phe Val Arg Pro  
275 280 285

5 Trp Ala Val Glu Lys Phe Ala Arg Val Trp Asp Cys Ile Pro Asp Ala  
290 295 300

10 Glu Thr Ala Leu Ser Ala Glu Glu Lys Ser His Ala Leu Val Thr Trp  
305 310 315 320

15 Leu Gln Ala Leu Val Asn Gln Leu Lys Leu Pro Asn Asn Leu Ala Ala  
325 330 335

Leu Gly Val Pro Pro Glu Asp Ile Ala Ser Leu Ser Glu Ala Ala Leu  
340 345 350

20 Asn Val Lys Arg Leu Met Asn Asn Val Pro Cys Gln Ile Asp Leu Gln  
355 360 365

25 Asp Val Gln Ala Ile Tyr Gln Thr Leu Phe Pro Gln His Pro Phe Lys  
370 375 380

Glu  
385

30 <210> 62  
<211> 105  
<212> PRT  
<213> Escherichia coli  
35 <400> 62

Met Asn Ile Arg Lys Leu Phe Cys Pro Gly Asn Thr Pro Arg Ile Leu  
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40 Leu Phe Leu Phe Phe Phe Val Val Ser Ala Ile Thr Thr Ile Ala Cys  
20 25 30

45 Gly Tyr Thr Glu Lys Asn Ala Thr Gly Asn Val Leu Leu Leu Phe Leu  
35 40 45

Leu Leu Leu Leu Ala His Arg Asn Thr Leu Thr Ser Ile Thr Ala Leu  
50 55 60

50 Leu Phe Leu Phe Cys Cys Ala Leu Tyr Ala Pro Ala Gly Met Thr Tyr  
65 70 75 80

55

# EP 1 342 784 A1

Gly Lys Ile Asn Asn Ser Phe Ile Val Ala Leu Leu Gln Thr Thr Thr  
 85 90 95

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 Asp Glu Ala Ala Glu Phe Thr Gly Met  
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 Leu Phe Ile Phe Phe Leu Ser Ser Ala Phe Val Ser Phe Gly Cys Tyr  
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25  
 Ala Ile Tyr Glu Leu Phe Leu Trp Asn Asp Ile Ile Val Tyr Ser Trp  
 35 40 45

30  
 Gly Tyr Ile Leu Ile Val Phe Leu Pro Phe Thr Leu Tyr Val Met Ser  
 50 55 60

35  
 Phe Glu Ile Leu Phe Phe Ala Ile Ser Gly Arg Arg Leu Ser Lys Val  
 65 70 75 80

40  
 Thr Met Val Arg Leu Trp Leu Ile Ile Lys Ile Ile Ile Ala Phe Ser  
 85 90 95

45  
 Ile Cys Ala Val Leu Ile Phe Ser Ser Ile Tyr Lys Lys Glu Leu Leu  
 100 105 110

50  
 Ser Arg Asn Tyr Ile Ala Cys Ser Gly Ile Pro Ser Gly Trp Met Pro  
 115 120 125

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 Gly Leu Ala Thr Lys Tyr Val Lys Glu Lys Ser Leu Cys Glu Lys Asn  
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Gly Asn Asn  
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<210> 64  
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EP 1 342 784 A1

<212> PRT  
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10 Leu Thr Val Val Leu Ser Gly Cys Gly Leu Ile Gln Lys Val Val Asp  
20 25 30

15 Glu Ser Lys Ser Val Ala Ser Ala Val Phe Tyr Lys Gln Ile Lys Ile  
35 40 45

20 Leu His Leu Asp Phe Phe Ser Arg Ser Ala Leu Asn Thr Asp Ala Glu  
50 55 60

25 Asp Thr Pro Leu Ser Thr Met Val His Val Trp Gln Leu Lys Thr Arg  
65 70 75 80

30 Glu Asp Phe Asp Lys Ala Asp Tyr Asp Thr Leu Phe Met Gln Glu Glu  
85 90 95

35 Lys Thr Leu Glu Lys Asp Val Leu Ala Lys His Thr Val Trp Val Lys  
100 105 110

40 Pro Glu Gly Thr Ala Ser Leu Asn Val Pro Leu Asp Lys Glu Thr Gln  
115 120 125

45 Phe Val Ala Ile Ile Gly Gln Phe Tyr His Pro Asp Glu Lys Ser Asp  
130 135 140

50 Ser Trp Arg Leu Val Ile Lys Arg Asp Glu Leu Glu Ala Asp Lys Pro  
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55 Arg Ser Ile Glu Leu Met Arg Ser Asp Leu Arg Leu Leu Pro Leu Lys  
165 170 175

Asp Lys

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EP 1 342 784 A1

Met Phe Leu Lys Arg Lys Trp Tyr Tyr Ala Val Thr Thr Ser Val Val  
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Ile Thr Leu Cys Gly Gly Gly Tyr Tyr Met Tyr Arg Gln Glu Tyr Gln  
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10  
Met Val Val Thr Val Pro Thr Ala Asp Ala Asn Asp Pro Asn Trp Pro  
35 40 45

15  
Asn Lys Arg Ile Gln Phe Asp Thr Ser Glu Trp Leu Gln Gln Leu Gln  
50 55 60

Tyr Ile Lys Ile Asp Asp His Tyr Ile Leu Asn Thr Gln Tyr Thr Pro  
65 70 75 80

20  
Ile Ala Asn Leu Asp Asp Phe Gly Ile Thr Leu Lys Leu Gln Asn Ala  
85 90 95

25  
Leu Asn Gly Ser Asp Lys Arg Leu Pro Ala Leu Tyr Gly Leu Ala Glu  
100 105 110

30  
Met Asp Ala Gln Lys Phe Lys Asp Leu Met Arg Gly Lys Ile Lys Cys  
115 120 125

Glu Tyr Leu Arg Thr Thr Phe Asp Ala Glu Thr Leu Lys Pro Val Asn  
130 135 140

35  
Asp Tyr Phe Leu Ile Ser Phe Thr Tyr Lys Asp Lys Trp Tyr Glu Phe  
145 150 155 160

40  
Glu Thr Glu Arg Lys Ile Ser Lys Thr Ser Asp Asp Gly Tyr Phe Leu  
165 170 175

45  
Trp Ala Phe Asp Asn Thr Val His Glu Ala Gly Tyr Trp His Asn Thr  
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Asp Pro Ala Ala Tyr Ser Tyr Arg Asp Tyr Gln Asn Gly Lys Ala Val  
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Lys

55

EP 1 342 784 A1

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 <212> PRT  
 <213> Escherichia coli  
 <400> 66

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Phe Arg Gln Tyr Val Phe Ser Leu Met Ser Ile Leu Leu Gln Glu Arg  
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Lys Met Asn Ile Phe Thr Leu Ser Lys Ala Pro Leu Tyr Leu Leu Ile  
 35 40 45

Ser Leu Phe Leu Pro Thr Met Ala Met Ala Ile Asp Pro Pro Glu Arg  
 50 55 60

Glu Leu Ser Arg Phe Ala Leu Lys Thr Asn Tyr Leu Gln Ser Pro Asp  
 65 70 75 80

Glu Gly Val Tyr Glu Leu Ala Phe Asp Asn Ala Ser Lys Lys Val Phe  
 85 90 95

Ala Ala Val Thr Asp Arg Val Asn Arg Glu Ala Asn Lys Gly Tyr Leu  
 100 105 110

Tyr Ser Phe Asn Ser Asp Ser Leu Lys Val Glu Asn Lys Tyr Thr Met  
 115 120 125

Pro Tyr Arg Ala Phe Ser Leu Ala Ile Asn Gln Asp Lys His Gln Leu  
 130 135 140

Tyr Ile Gly His Thr Gln Ser Ala Ser Leu Arg Ile Ser Met Phe Asp  
 145 150 155 160

Thr Pro Thr Gly Lys Leu Val Arg Thr Ser Asp Arg Leu Ser Phe Lys  
 165 170 175

Ala Ala Asn Ala Ala Asp Ser Arg Phe Glu His Phe Arg His Met Val  
 180 185 190

Tyr Ser Gln Asp Ser Asp Thr Leu Phe Val Ser Tyr Ser Asn Met Leu  
 195 200 205

EP 1 342 784 A1

Lys Thr Ala Glu Gly Met Lys Pro Leu His Lys Leu Leu Met Leu Asp  
 210 215 220  
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 Gly Thr Thr Leu Ala Leu Lys Gly Glu Val Lys Asp Ala Tyr Lys Gly  
 225 230 235 240  
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 Thr Ala Tyr Gly Leu Thr Met Asp Glu Lys Thr Gln Lys Ile Tyr Val  
 245 250 255  
 Gly Gly Arg Asp Tyr Ile Asn Glu Ile Asp Ala Lys Asn Gln Thr Leu  
 260 265 270  
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 Leu Arg Thr Ile Pro Leu Lys Asp Pro Arg Pro Gln Ile Thr Ser Val  
 275 280 285  
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 Gln Asn Leu Ala Val Asp Ser Ala Ser Asp Arg Ala Phe Val Val Val  
 290 295 300  
 25  
 Phe Asp His Asp Asp Arg Ser Gly Thr Lys Asp Gly Leu Tyr Ile Phe  
 305 310 315 320  
 Asp Leu Arg Asp Gly Lys Gln Leu Gly Tyr Val His Thr Gly Ala Gly  
 325 330 335  
 30  
 Ala Asn Ala Val Lys Tyr Asn Pro Lys Tyr Asn Glu Leu Tyr Val Thr  
 340 345 350  
 35  
 Asn Phe Thr Ser Gly Thr Ile Ser Val Val Asp Ala Thr Lys Tyr Ser  
 355 360 365  
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 Ile Thr Arg Glu Phe Asn Met Pro Val Tyr Pro Asn Gln Met Val Leu  
 370 375 380  
 Ser Asp Asp Met Asp Thr Leu Tyr Ile Gly Ile Lys Glu Gly Phe Asn  
 385 390 395 400  
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 Arg Asp Trp Asp Pro Asp Val Phe Val Glu Gly Ala Lys Glu Arg Ile  
 405 410 415  
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 Leu Ser Ile Asp Leu Lys Lys Ser  
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EP 1 342 784 A1

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 <211> 489  
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 agtggatctc catgggttaa ttttgatctg tctctcaccg gatgccagaa tatgaatact 240  
 gttcgggcaa catttagtgg tactgaggat gggcagacat actatgcgaa tacagggaaat 300  
 15 gctggcggtta tcaagattga aattcaggac agggatggaa gtaatgcac atatcacaat 360  
 ggtatgttca agacgcttaa tgtacaaaat aataatgcaa cctttaatct taaagcccgt 420  
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 20 acctatgcg 489  
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 25 <211> 2019  
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 gacgcggcg tcaccgccag cgacaaactc cccagagtct tgcccgggct caatattgaa 240  
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 ttctataacc ccgcgctcac cctgtatgtc gatggcgctc ctcagctttc caccaacacc 360  
 atccaggcgc ttaccgatgt gcaaagcgtg gagttgctgc gagggccaca gggaacgtta 420  
 40 tatggcaaaa gcgctcaggg cgggatcacc aacatcgta cccagcagcc ggacagcacg 480  
 ccgcgcggct atattgaagg cggcgctcag agccgcgaca gttatcgaag taagttcaac 540  
 45 ctgagcggcc ccattcagga tggcctgctg tacggcagcg tcaccctgtt acgccagggt 600  
 gatgacggcg acatgattaa ccccgcgacg ggaagcgatg acttaggcg caccgcgccc 660  
 agcatagggg atgtgaaact gcgtctggcg ccggacgacg agccctggga aatgggcttt 720  
 50 gccgcctcac gcgaatgtac ccgcgccacc caggacgcct atgtgggatg gaatgatatt 780  
 aagggccgta agctgtcgat cagcgatggt tcaccagacc cgtacatgcg gcgctgcact 840  
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# EP 1 342 784 A1

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	accgttgata tgggtgtttgg gctgtaccgg cagaacaccc gcgagaagtt aaattcagcc	1080
	tacgacatgc cgacaatgcc ttattttaagc agtaccggct ataccaccgc tgaaacgctg	1140
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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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## EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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EP 1 342 784 A1

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# EP 1 342 784 A1

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**Claims**

1. Isolated antigenic polypeptides selected in the group comprising SEQ ID N°11 to SEQ ID N°66 and the homologous sequences.
2. Isolated antigenic polypeptides according to claim 1 obtainable by a process comprising the steps of:
  - 1- selecting on the basis of sequence analysis those of the polypeptides which are either located in the outermembrane or secreted by the bacteria,
  - 2- identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates,
  - 3- purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in B2/D isolates,
  - 4- testing the polypeptides for immunogenicity using animals models.
3. Isolated polynucleotides, coding for a polypeptide according to claim 1 or 2, according to the universal genetic code.
4. Isolated polynucleotides according to claim 3, having sequences selected in the group comprising SEQ ID N°77 to SEQ ID N°132.
5. An expression vector comprising at least an isolated polynucleotide according to claim 3 or 4.
6. A host cell comprising an expression vector according to claim 5.
7. A process for isolating and identifying antigenic polypeptides, useful as vaccines comprising the steps of:
  - 1- selecting on the basis of sequence analysis those of the polypeptides which are either located in the outermembrane or secreted by the bacteria,
  - 2- identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates,
  - 3- purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in B2/D isolates,
  - 4- testing the polypeptides for immunogenicity using animals models.
8. The process of claim 7, comprising the use of infected adult animals, eventually immunodepressed, and of infant animals as models for neonatal infections.
9. The use of at least one polypeptide selected in the group comprising SEQ ID N°1 to SEQ ID N°66 as antigens and the homologous sequences.
10. A vaccine composition specific to *E. coli* extra-intestinal infections, comprising an effective amount of at least one antigenic polypeptide such as selected by the process of claim 7, alone or in combination, particularly at least one polypeptide having a sequence selected in the group comprising SEQ ID N°1 to SEQ ID N°66 and the homologous sequences, with a carrier.
11. The vaccine composition of claim 10 for preventing urinary system infections, pyelonephritis, sepsis, bacteremia, neonatal meningitis.
12. The vaccine composition of claim 10 or 11, adapted to specific indication in combination with components directed against other bacteria, such as *S.aureus* or group B *Streptococcus*.
13. Antibodies or fragments thereof directed against a polypeptide such as used according to claim 9.
14. A method for detecting the present or absence of undesirable extra-intestinal *E. coli*, and/or for the diagnosis of an extra-intestinal *E. coli* infection, comprising the use of at least one polypeptide such as defined in claim 9, or a polynucleotide according to claim 3 or 4, or an antibody to claim 13.
15. Pharmaceutical composition for alleviating and/or preventing and/or treating and undesirable growth of *E. coli* comprising an effectiveness of at least one polypeptide such as use in claim 9.



European Patent  
Office

# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention Ep 02 29 0556  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 01 66572 A (INST NAT SANTE RECH MED ;NASSIF XAVIER (FR); TINSLEY COLIN (FR); B) 13 September 2001 (2001-09-13) SEQ ID NOs:347 and 348 * page 3, line 20 - page 4, line 17 * * page 29, line 23 - line 31 *	1-6,9-15	C12N15/31 C12N15/63 C07K14/245 C07K16/12 A61K39/108 G01N33/53
A	JOHNSON JAMES R ET AL: "Phylogenetic and pathotypic similarities between Escherichia coli isolates from urinary tract infections in dogs and extraintestinal infections in humans." JOURNAL OF INFECTIOUS DISEASES, vol. 183, no. 6, 2001, pages 897-906, XP002211433 ISSN: 0022-1899 * abstract *		
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C12N C07K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		28 August 2002	Mata-Vicente, M
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p>			

EPO FORM 1503 03/82 (P0407)



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INCOMPLETE SEARCH  
SHEET C

Application Number  
EP 02 29 0556

As far as an "in vivo" method is concerned claim 9 is directed to a method of treatment of the human/animal body (Article 52(4) EPC) and the search has been carried out and based on the alleged effects of the compound/composition.

As far as an "in vivo" method is concerned claim 14 is directed to a diagnostic method practised on the human/animal body (Article 52(4) EPC) and the search has been carried out and based on the alleged effects of the compound/composition.





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Office

## PARTIAL EUROPEAN SEARCH REPORT

Application Number  
EP 02 29 0556

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<p>MUEHLDORFER I ET AL: "Characterization of Escherichia coli strains isolated from environmental water habitats and from stool samples of healthy volunteers." RESEARCH IN MICROBIOLOGY, vol. 147, no. 8, 1996, pages 625-635, XP002211434  ISSN: 0923-2508  * table 1 *  * page 630, paragraph 2 *  -----</p>		
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03/92 (P04C10)



European Patent  
Office

Application Number

EP 02 29 0556

### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- (1-6 and 9-15) partially



European Patent  
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LACK OF UNITY OF INVENTION  
SHEET B

Application Number  
EP 02 29 0556

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 1: Claims (1-6 and 9-15) - partially

Isolated antigenic polypeptide SEQ ID NO:11; the polynucleotide encoding it (SEQ ID NO:77); vector comprising said polynucleotide and host cell transformed with it; antibodies against said polypeptide; vaccines comprising the polypeptide; methods of diagnosis/treatment derived of the use of any of the molecules previously mentioned.

Inventions 2-56: Claims (1-6 and 9-15) - partially

Idem as invention 1, but restricted to each one of the polypeptides of SEQ ID NOs:12-66 and and their corresponding genes (SEQ ID NOs:78-132).

Invention 57: Claims (9-15) - partially

Use of the polypeptide SEQ ID NO:1 as antigen; vaccines; antibodies against said polypeptide; methods of diagnosis/treatment derived of the use thereof.

Inventions 58-66: Claims (9-15) - partially

Idem as invention 57, but restricted to each one of the polypeptides SEQ ID NOs:2-10.

Invention 67: Claims (7 and 8) - partially

Process for isolating and identifying polypeptides useful as vaccines comprising the steps of: selecting on the basis of sequence analysis those of the polypeptides which are either located in the outer membrane or secreted by the bacteria; identifying the genes coding for said polypeptides which are conserved in B2/D clinical isolates; purifying the polypeptides identified in step 1, which are found in step 2 to be conserved in B2/D isolates; and testing the polypeptides for immunogenicity using animal models.

EP 02 29 0556

28-08-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0166572 A	13-09-2001	FR WO 2806096 A1 0166572 A2	14-09-2001 13-09-2001
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EPO FORM 90458

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2005/002105

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/108 A61K39/10 A61K39/112 A61K39/106 A61K39/39  
A61K39/02 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, Sequence Search, BIOSIS, WPI Data, PAJ, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 342 784 A (MUTABILIS S.A) 10 September 2003 (2003-09-10) paragraph '0031! - paragraph '0034! claim 10 sequence 9	1-10
A	DATABASE UniProt 'Online! 1 November 1996 (1996-11-01), "Cytotoxic necrotizing factor 1." XP002323706 retrieved from EBI accession no. UNIPROT:Q47106 Database accession no. Q47106 the whole document	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

24 June 2005

Date of mailing of the international search report

26.08.2005

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2005/002105

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MOREAU VIOLAINE ET AL: "Actin can reorganize into podosomes in aortic endothelial cells, a process controlled by Cdc42 and RhoA." MOLECULAR AND CELLULAR BIOLOGY, vol. 23, no. 19, October 2003 (2003-10), pages 6809-6822, XP002323705 ISSN: 0270-7306 abstract page 6810, left-hand column, paragraph 6</p>	1-10
T	<p>MUNRO P ET AL: "The Rho GTPase activators CNF1 and DNT bacterial toxins have mucosal adjuvant properties" VACCINE, BUTTERWORTH SCIENTIFIC, GUILDFORD, GB, vol. 23, no. 20, 8 April 2005 (2005-04-08), pages 2551-2556, XP004789509 ISSN: 0264-410X the whole document</p>	1-9

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2005/002105

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10 (completely)

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-10 (all completely)

A vaccine composition comprising an immunoadjuvant compound consisting of a Rho GTPase activator.

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Invention 2: claims 11-13 (all partially)

A protein comprising a polypeptide consisting of the injection domain of a Rho GTPase activator comprising residues 1-719 of SEQ ID No. 1 and the catalytic domain of a Rho GTPase activator comprising residues 720-1014 of SEQ ID No. 1; the use of said polypeptide or of a polypeptide according to SEQ ID No. 1 for manufacturing a vaccine composition.

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Invention 3-4: claims 11-13 (all partially)

Idem as invention 3, but each of invention 3 and 4 referring to SEQ ID Nos. 2 and 3, respectively.

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Invention 5: claims 11-13 (all partially)

A protein comprising a polypeptide consisting of the injection domain of a Rho GTPase activator comprising residues 1-1145 of SEQ ID No. 4 and the catalytic domain of a Rho GTPase activator comprising residues 1145-1451 of SEQ ID No. 4; the use of said polypeptide or of a polypeptide according to SEQ ID No. 4 for manufacturing a vaccine composition.

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Inventions 7-10: claim 11-13 (partially)

Idem as invention 6, but each of the inventions 7-10 referring to one of SEQ ID Nos. 6-9.

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